

ANGLIA RUSKIN UNIVERSITY

EFFECT OF SLOW AND DEEP BREATHING ON CLINICAL BLOOD PRESSURES  
AND A PILOT STUDY ON ITS EFFECTIVENESS IN PREGNANT WOMEN

NWOBODO NZERIBE, NNENNA HARMONY

A thesis in partial fulfilment of the requirements of  
Anglia Ruskin University for the degree of MPhil in  
Medical Technology

This research was carried out  
In collaboration with Newcastle University, United Kingdom  
and Enugu State University Teaching Hospital, Parklane, Enugu, Nigeria

Submitted: August 2016

## **Acknowledgement**

In accomplishing this work, I am greatly indebted to my supervisor Dr. Dingchang Zheng for his advice and unflinching encouragement even at odd hours. I also owe a lot to Prof. Richard Aspinall who is my second supervisor and all the academic and non-academic staff of Postgraduate Medical Institute, Faculty of Medical Sciences, Anglia Ruskin University (ARU), Chelmsford, United Kingdom.

I also appreciate Jo Corney, Faculty Research Administrator, especially for her availability, constant advice and support during the course of this study. My profound attitude also goes to Allen Mugasha and the entire staff of Postgraduate Research School for all the research training they offered. The assistance granted to me by the IT unit and study skill centers is not forgotten. To all the library staff, I say thank you for all the assistance you granted to me.

My gratitude also goes to Shauna, Elvis and all the International student bodies of ARU for creating a conducive atmosphere for me to study as an international student. Thanks also to the student union department for making us feel as part of them.

My regard also goes to my parents H.R.H and Lolo Felix Nwobodo Ani, my brothers and sisters who did not cease in praying and encouraging me both emotionally and financially.

Thanks also to my colleagues in this work Syed, Natalia, Ibrahim and Chris who kept lifting my spirit up that we will make it together.

Most importantly to appreciate is TETFUND (Tertiary Funding) of Nigeria Universities for this opportunity they gave me, through ESUT (Enugu State University of Science and Technology) to explore academics experience in this dimension. I highly appreciate all the staff of ESUT. My thanks also goes to the Cardiovascular Physics and Engineering Research Group at Newcastle University, United Kingdom for the data collection of study 1 in this work.

Finally, I praise my husband, Charles and children (Olivia, Destiny, Emmanuella and Triumph), who gave me their love and appreciation, and never complained throughout my stay in the United Kingdom and when I could not meet up with domestic needs in pursuit of this study. May God bless you all, Amen.

ANGLIA RUSKIN UNIVERSITY  
ABSTRACT

FACULTY OF MEDICAL SCIENCES

MASTERS OF PHILOSOPHY

EFFECT OF SLOW AND DEEP BREATHING ON CLINICAL BLOOD PRESSURES  
AND A PILOT STUDY ON ITS EFFECTIVENESS IN PREGNANT WOMEN

NWOBODONZERIBE NNENNA HARMONY

August 2016

There is no study investigating the effect of deep breathing on clinical BPs measured simultaneously by manual auscultatory and automatic techniques. This research aimed to provide scientific evidence on the comparison of the effect of deep breathing on manual auscultatory BPs and automatic BPs, and will also preliminarily investigate the effect of deep breathing on pregnant subjects.

The first study involved thirty-nine healthy subjects. The manual systolic and diastolic BPs (SBP and DBP) and MAP were obtained from each subject under resting and deep breathing conditions. During the manual measurement, the oscillometric cuff pressure was simultaneously recorded to determine automated SBP, MAP and DBP, which were cuff pressures corresponding to 50%, 100% and 70% of the waveform envelope, fitted to the oscillometric pulse amplitude. Finally, the effect of deep breathing on both manual and automated BPs were compared.

Experimental results showed that deep breathing significantly (all  $p < 0.001$ ) decreased manual SBP, MAP and DBP by 3.5, 3.7 and 3.7 mmHg, respectively, when compared with the resting condition. Automated SBP, MAP and DBP were also decreased significantly (all  $p < 0.001$ ) by 2.0, 3.4 and 3.2 mmHg, respectively. In addition, it is observed that 56%, 62% and 67% of subjects showed SBP, MAP and DBP reductions with deep breathing in both manual auscultatory and automatic oscillometric techniques.

The second study involved twenty pregnant subjects. Automated SBP and DBP were measured from each subject at different time points (before, during and after deep breathing). The automated BPs were then compared between the different time points. Experimental results showed that deep breathing decreased automated SBP and DBP significantly ( $p < 0.001$ ) by 6.4 and 4.8 mmHg. Similarly, automated SBP and DBP measured after deep breathing were also significantly ( $p < 0.001$ ) decreased by 5.6 and 4.5 mmHg, respectively. Over 70% of the subjects had either SBP or DBP reduction during and after deep breathing.

In conclusion, both manual and automatic BPs were significantly decreased with deep breathing. Over half of the normal healthy subjects achieved significant BP reductions with deep breathing in both manual and automatic techniques. Additionally, it has been demonstrated by our pilot study that deep breathing can be potentially used as a management tool to reduce BPs for some pregnant women.

**Keywords:** Deep breathing, Pregnancy Induced Hypertension (PIH), Diastolic Blood Pressure (DBP), Systolic Blood Pressure (SBP), Mean Arterial Pressure (MAP), Automated, Manual

## Table of Contents

Acknowledgement .....	i
List of figures.....	iv
List of tables.....	v
List of abbreviations .....	vi
CHAPTER 1 Blood Pressure (BP) and its measurement techniques.....	1
1.1 General overview of BP .....	1
1.2 Classification of BP.....	2
1.3 Non-pharmacological treatment of hypertension .....	5
1.4 BP measurement and its importance .....	9
1.5 BP measurement techniques.....	11
1.6 Manual auscultatory technique.....	13
CHAPTER 2 Pregnancy Induced Hypertension (PIH) and its management .....	19
2.1 General overview of PIH.....	19
2.2 Diagnosis of PIH .....	24
2.3 Management of PIH .....	24
2.4 Pharmacological treatment of PIH .....	28
2.5 Non-pharmacological treatment of PIH using respiratory exercise .....	28
2.6 Aims and objectives of this research.....	32
2.7 Organization of this thesis.....	33
CHAPTER 3 Methodology and data analysis.....	35
3.1 Study 1: Simultaneous effect of deep breathing on manual and automated BPs.....	35
3.2 Study 2: Effect of deep breathing on automatic BP of pregnant women.....	40
CHAPTER 4 Results.....	43
4.1 Results from study1:.....	43
4.2 Results from study 2: (Effect of deep breathing on BP of pregnant women) .....	48
CHAPTER 5 Discussion, conclusion and future work .....	55
5.1 Conclusion.....	55
5.2 Discussion .....	55
5.3 Limitations and challenges.....	57
5.4 Recommendations for future study .....	58
References.....	59

## List of figures

Figure 1.1	Chart for easy BP classification .....	3
Figure 1.2	Process of inhalation and exhalation.....	6
Figure 1.3	Different techniques of deep breathing.....	7
Figure 1.4	BP measurement by a clinician.....	9
Figure 1.5	Diagram of BP measurement techniques.....	11
Figure 1.6	Invasive BP measurement technique.....	12
Figure 1.7	Mercury Sphygmomanometer.....	15
Figure 1.8	Aneroid Sphygmomanometer.....	16
Figure 1.9	Illustration of automated BP determination method .....	17
Figure 1.10	Automatic BP devices.....	17
Figure 2.1	Development of preeclampsia during pregnancy.....	21
Figure 2.2	Typical signs and symptoms of PIH.....	22
Figure 3.1	Block diagram of measurement system of study 1 .....	37
Figure 3.2	Schematic diagram of BP measurement for study 1.....	37
Figure 3.3	BP measurement protocol of study 1.....	37
Figure 3.4	Schematic diagram of data analysis procedure for study 1 .....	39
Figure 3.5	Block diagram of BP measurement system for study 2.....	40
Figure 3.6	Measurement protocol of study 2.....	41
Figure 3.7	Block diagram of BP data comparison for the three conditions.....	42
Figure 4.1	Manual and automated BP under resting and deep breathing conditions.....	44
Figure 4.2	Bland-Altman plots for the BP changes with deep breathing.....	46
Figure 4.3	Example of oscillometric waveforms illustrating decreased automated BP with deep breathing in comparison to resting condition.....	46
Figure 4.4	Comparison of manual and automated BP decrease.....	47
Figure 4.5	Bland-Altman plots between automatic and manual BP technique.....	48
Figure 4.6	Bland-Altman plots between repeated measurement.....	50
Figure 4.7	Comparison of automated BPs (before, during and after deep breathing).....	52
Figure 4.8	Individual SBP changes during and after deep breathing.....	53
Figure 4.9	Individual DBP changes during and after deep breathing.....	54

## List of tables

Table 1.1	Different breathing patterns.....	6
Table 2.1	Classification of PIH.....	20
Table 2.2	Signs and symptoms of PIH.....	23
Table 2.3	Summary of diagnostic tests of PIH.....	26
Table 2.4	Management of PIH.....	27
Table 2.5	Antihypertensive drugs on pregnancy.....	29
Table 2.6a	Past studies on effect of deep breathing on BP.....	30
Table 2.6b	Summary of past studies on effect of deep breathing on BP .....	31
Table 4.1	Demographic data of the subjects in study 1.....	43
Table 4.2	Overall mean and SD of BPs under resting and deep breathing conditions.....	44
Table 4.3	Demographic data of pregnant women in study 2.....	49
Table 4.4	Mean and SD of BP measurement repeatability.....	49
Table 4.5	Mean and SD of automated BP before, during and after deep breathing.....	51

## List of abbreviations

ACE	Angiotensin-Converting Enzyme inhibitor
ACOG	American College of Obstetricians and Gynaecologists
ADA	American Diabetes Associate
AHA	American Heart Association
ANOVA	Analysis of Variables
ARB	Angiotensin Receptor Blocker
ASA	American and Stroke Association
ASSHP	Australasian Society for the Study of Hypertension in Pregnancy
BHS	British Hypertension Society
BP	Blood pressure
CCB	Calcium Channel Blocker
CHS	Canadian Hypertension Society
DBP	Diastolic Blood Pressure
ERS	European Respiratory Society
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESUT	Enugu State University of Science and Technology
FDA	Food and Drug Administration
FFR	Frequency Following Response
GH	Gestational Hypertension
HELLP	Haemolysis Elevated Liver and Low Platelets
Inc	Incorporated
ISH	International Society of Hypertension
ISO	International Standard Organization
JNC	Joint National Committee
JNCDETH	Joint National Committee on Detection, Evaluation, and Treatment of High blood pressure
JSH	Japan Society of Hypertension
MAP	Mean Arterial Pressure
MATLAB	Matrix Laboratory
NHBPEP	National High Blood Pressure Education Program
NICE	National Institute of Health Care

PE	Preclampsia
PIH	Pregnancy Induced Hypertension
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEM	Standard Error Mean
SPSS	Statistical Products and Software Solution
WHO	World Health Organisation
UK	United Kingdom
USA	United States of America
TETFUND	Tertiary Funding



## **CHAPTER 1      Blood Pressure (BP) and its measurement techniques**

This chapter gives a general overview of BP and its measurement techniques. The treatment of hypertension is also discussed with emphasis on non-pharmacological treatment using respiratory exercise.

### **1.1      General overview of BP**

Blood pressure (BP) is one of the most regularly recorded clinical parameters in human physiological studies for over 250 years, for both clinical and research purposes (Shapiro, et al., 1996; Pickering, et al., 2005). In 1711, BP was observed by Stephen Hales, a Church of England clergyman, who assumed that blood should be under pressure to circulate. He proved his hypothesis by penetrating a hollow brass glass tube needle into the artery of a horse leg, and observed that there was a regular rise of blood in the hollow brass glass tube. This observation has been recorded in a book titled “Statistical Essays” in 1733 (Wood and Griffith, 1997).

Generally speaking, BP is associated with arterial pressure as it pumps blood from the heart to other parts of the body (Wood and Griffith, 1997; Fahey, et al. 2004; Martini and Nath, 2009). The heart is the major blood pumping organ. It circulates blood to other parts of the body through the arteries and arterioles. During the process, oxygen and food substances are transported to the body, while carbon dioxide and other waste products are excreted out. The whole circulation process relies on blood being under pressure (Fahey, et al. 2004).

As the heart regularly pumps blood out, the muscles in walls of arteries and arterioles contract and expand during blood circulation. When the heart contracts to pump blood to the body, pressure is at its highest point. When the heart relaxes and expands to be filled with blood, pressure is at its lowest point. The highest pressure point of BP is known as the systolic blood pressure (SBP) while the lowest pressure point is known

as the diastolic blood pressure (DBP) (Wood and Griffith, 1997). On the other hand, as the heart beats, BP varies at different sites in the body. It is higher at the aorta and large systemic arteries and relatively lower at the venules and veins (Tortora and Derrickson, 2007; Davies, Blakeley and Kidd 2011).

BP is normally expressed in millimetres of mercury (mmHg) and recorded as a fraction, having SBP as the numerator and DBP as the denominator. It is generally written as SBP/DBP (Seeley, et al., 1995; Poulter, Thom and Kirby, 2001).

## **1.2 Classification of BP**

BP is classified into low BP, normal BP, pre-high BP and high BP, depending on the readings of SBP and DBP. BP readings vary from person to person, and from time to time. It may also depend on the posture, exercise and stress of an individual. Figure 1.1 shows a BP chart for easy classification of BP. The vertical axis represents the SBP which ranges from 50 to 170 in mmHg while the horizontal axis represents the DBP which ranges from 30 to 100 mmHg. The figure is also indicated by colour to determine normal BP (green), high BP (red), pre- high BP (orange) and low BP (blue) (Petrie, et al., 1986; National High Blood Pressure Education Program, 2004; Blood pressure UK, 2008; Sharman et al., 2016)

### **a) Normal BP**

Normal BP occurs when SBP reading is between the range of 80 to 110 mmHg and DBP is between 60 to 80 mmHg. To keep normal BP, reduction in salt intake, eating of more fruit and vegetables, keeping to alcohol limit and taking of regular exercise are recommended (National High Blood Pressure Education Program, 2004; Blood pressure UK, 2008; Sharman et al., 2016).

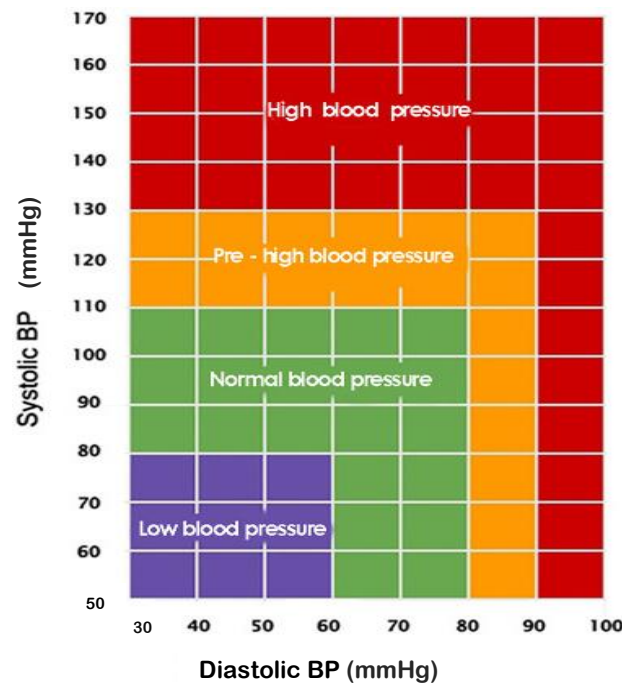


Figure 1.1: Chart for easy BP classification (Blood pressure UK, 2008).

#### b) Low BP

Low BP, also known as hypotension, is diagnosed when BP reading is consistently lower than 80/60 mmHg. Low BP usually occurs as postural hypotension. For instance, when one stands up normally, blood rushes to lower extremities part of the body like the feet and fingers, which, if not controlled, could cause BP to fall, to offset these blood pools. The body normally reacts involuntarily to control it, by alerting the heart to beat faster and the blood vessels to constrict. If the reaction does not happen or occurs too slowly, postural hypotension occurs (Petrie, et al., 1986; Blood pressure UK, 2008). Postural hypotension is commonly noticeable in people aged above 60 years old, especially in patients with diabetes.

In addition, low BP could occur when the neck BP is not sufficient enough to supply the oxygen and glucose to support the maximal function of the brain. It occurs easily and often in teenage girls, because they commonly have SBP below 100 mmHg (Petrie, et al., 1986; Fahey, Murphy and Hart, 2004; Sharman et al., 2016).

Low BP can be overcome by adding more salt to diet, being well hydrated, standing up gradually, avoiding standing for a long period of time and wearing of support stockings (Fahey, Murphy and Hart, 2004). Arising slowly from sitting position, performing isometric (hand grip) exercise before arising, eating small breakfast, and drinking two large glasses of water early in the morning are also suggested (Kaplan, 2001).

### **c) High BP**

High BP, also known as hypertension, is when BP readings are measured consistently for a number of weeks at 140 mmHg or above for SBP, and 90 mmHg or above for DBP. A single 140/90 mmHg reading at a particular time is not enough to conclude the diagnosis of high BP. More than two extra readings of such BP measurements are needed to be monitored over time. When a pregnant woman develops hypertension, it is known as Pregnancy Induced Hypertension (PIH) (Rolleston and Camb, 2007; Sharman et al., 2016).

BP readings that persist consistently between (120/80) mmHg and (140/90) mmHg is known as Pre-high BP. Readings of 180/90 mmHg or higher indicates a hypertensive crisis (Petrie, et al., 1986; Fahey, Murphy and Hart, 2004; MacGregor and Kaplan, 2006; Sharman et al., 2016). Symptoms like severe headache, fatigue, confusion, problems associated with vision, chest pain, pounding in the chest, neck or ears, breathing difficulty and blood in urine could indicate the presence of extreme high BP. Persistent hypertension could lead to diseases like kidney failure, stroke or dementia, eye problems and heart disease (Rolleston and Camb, 2007).

Hypertension can be treated by drugs like methyldopa, clonidine, labetalol, hydralazine or oxprenolol, nifedipine, atenolol, verapamil, nitroprusside, thiazide, spironolactone etc. It can also be overcome by weight reduction, regular physical exercise, limited alcohol consumption, stopping smoking, low intake of total and saturated fats, low

intake of dietary salts and overall increase of fruits and vegetable intake (Poulter, et al. 2001; Williams, et al., 2004).

### **1.3 Non-pharmacological treatment of hypertension**

Deep breathing has been widely accepted as one of the key factors imposing a physiological change in BP (Zheng et al., 2012). The following sections will give a general overview on breathing and discuss how deep breathing affects BP.

#### **1.3.1 Breathing**

Breathing is the mechanism during which air is inhaled into the lungs and then exhaled via the nose or mouth. Two processes involved during breathing are inspiration and expiration. Normal breathing also called apnea is involuntary and rhythmic (Moini, 2012; Martini and Bartholomew, 2007).

##### **a) Inspiration or inhalation**

As shown in figure 1.2, inspiration or inhalation involves taking oxygen into the body. During inspiration, intercostal muscles between the ribs contract, and get the ribs raised upward and outward, the ribcage is then expanded. Also, the diaphragm contracts, flattens, pulls down, and causes an increase in thorax volume. This lowers the pressure inside the thorax and gets air sucked into the lungs (Martini and Nath, 2009; Moini, 2012).

##### **b) Expiration or exhalation**

Expiration or exhalation takes carbon dioxide out of the body. During exhalation, intercostal muscles relax and lower the ribs downward, causing the diaphragm to relax and move back upwards. This causes a decrease in thorax volume, which as a result, increases the pressure inside the thorax and forces air out of the lungs (Martini and Nath, 2009; Moini, 2012).

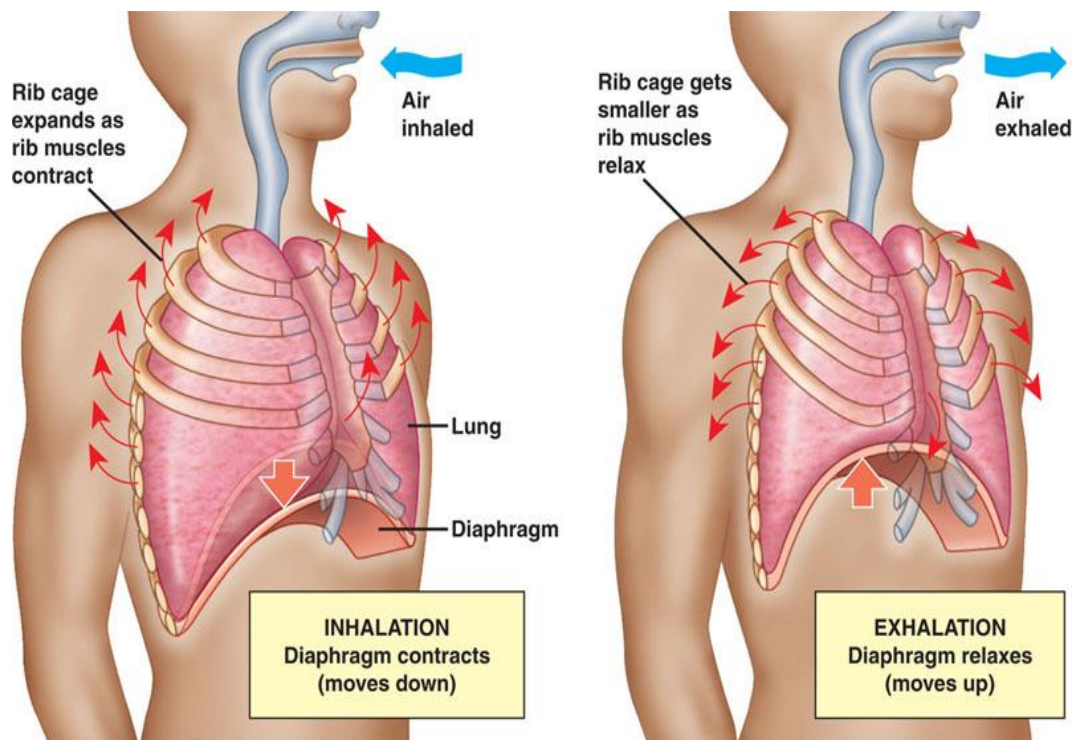











Figure 1.2: Process of inhalation and exhalation (Martini and Bartholomew, 2007).

### 1.3.2 Types of breathing

Breathing pattern is characterized by the rate, depth, timing and consistency of breaths during inhalation and exhalation processes. It differs between individuals depending on their health condition. Table 1.1 shows some typical breathing patterns with brief description (Thibodeau, 2010; Hubbard and Falco, 2015).

Table 1.1: Different breathing patterns (Thibodeau, 2010).

	Condition	Description	Causes
	Eupnea	Normal breathing rate and pattern	
	Tachypnea	Increased respiratory rate	Fever, anxiety, exercise, shock
	Bradypnea	Decreased respiratory rate	Sleep, drugs, metabolic disorder, head injury, stroke
	Apnea	Absence of breathing	Deceased patient, head injury, stroke
	Hyperpnea	Normal rate, but deep respirations	Emotional stress, diabetic ketoacidosis
	Cheyne-Stokes	Gradual increases and decreases in respirations with periods of apnea	Increasing intracranial pressure, brain stem injury
	Biot's	Rapid, deep respirations (gasps) with short pauses between sets	Spinal meningitis, many CNS causes, head injury
	Kussmaul's	Tachypnea and hyperpnea	Renal failure, metabolic acidosis, diabetic ketoacidosis
	Apneustic	Prolonged inspiratory phase with shortened expiratory phase	Lesion in brain stem

### 1.3.3 Deep breathing

Deep breathing is performed by narrowing the diaphragm and expanding the abdomen. During the process, air enters via the nose, fills the lungs and then expands the lower belly. It is sometimes called diaphragmatic breathing or belly breathing. Figure 1.3 shows different techniques of deep breathing, which can be performed on lying or sitting down positions. During deep breathing, maximal amount of oxygen is transferred to the blood stream, which triggers relaxation. Deep breathing is applied in order to calm the body down because it strengthens and triggers the parasympathetic system (Fried, 1993; Mason, et al., 2013; Pattanshetty and Thapa, 2015).



Figure 1.3: Different techniques (lying and sitting down) of deep breathing (Adopted from Sisson, 2012; Raisingchildren, 2014).

### 1.3.4 Steps involved in practice of deep breathing

The steps involved in practicing deep breathing include:

- 1) Find a calm or quiet place;
- 2) Lie down in a supine position, keep back and neck straight, pull the abdomen and breathe in through the nose (count 1,2,3,4 as you inhale if possible). Allow the belly

to expand as the air move in. Allow the expansion to continue upwards towards the chest;

- 3) Exhale slowly without forcing air out from your lungs. Try to exhale for the same duration of inhaling air (count 1, 2, 3, 4);
- 4) 3 seconds inhale and 3 seconds exhale of deep breathing is recommended at a start. Extend the length of time of inhale and exhale for each breath, up to 5 seconds. This could get into 6 cycles per minute;
- 5) Finally, repeat the cycle for several minutes.

### **1.3.5 How deep breathing affects BP**

It has been generally accepted that deep breathing reduces BP. The underlying physiological mechanisms of the effect of deep breathing on BP include: (Guyton, 1961; Hubbard and Falco, 2015)

Firstly, deep breathing makes the blood more alkaline. With enough oxygen into the body, it makes the kidney more efficient in removing sodium from the blood, triggering lower BP (Guyton, 1961; Hubbard and Falco, 2015).

Secondly, high BP is associated with blocked nitric oxide embedded in the endothelial cells of the blood vessels. During deep breathing, there is an increase in transmission of nitric oxide. The blood cells utilize the nitric oxide to communicate to the blood vessels to naturally relax during vasodilation. This results in increase of blood flow as well as reduction of BP (Hubbard and Falco, 2015).

Thirdly, any slight deviation in the oxygen content in the brain affects the feeling and behaviour of an individual. During deep breathing, oxygenation allows the body to absorb its full oxygen quota, which relaxes the brain and calms the cardiovascular system, resulting in reduced stress and decreased BP (Guyton, 1961; Hubbard and Falco, 2015).



### 1.3.6 Device guided breathing

Several devices have been developed to guide inhalation and exhalation rhythm during deep breathing exercise. It has been reported by Rosenthal, et al., (2000, 2001) and Viskoper, et al. (2003) that BPs could be reduced during deep breathing with a guided device. RESPeRATE is the first guided breathing device that has been clinically approved to lower BP (Cernes and Zimlichman, 2015). Recently, the Food and Drug Administration (FDA) has approved breathing device as a treatment for lowering both stress levels and BP (Sharman, et al., 2011; Cernes and Zimlichman, 2015).

## 1.4 BP measurement and its importance

Hypertension is among the most common chronic medical disorders, which can destroy cardiovascular organs, if ignored. Accurate, routine and reliable BP measurement is therefore essential for medical diagnosis and for monitoring response to therapy (Poulter, Thom and Kirby, 2001). Figure 1.4 shows a BP measurement by a clinician.

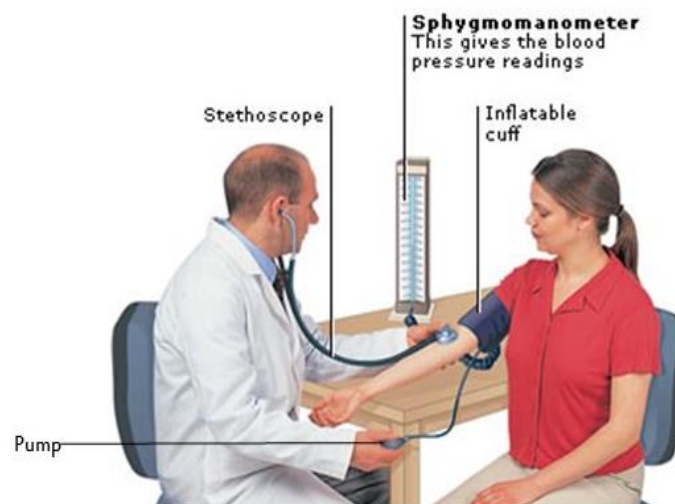


Figure 1.4: BP measurement by a clinician (Farziana, et al., 2009).

Unfortunately, BP measurement error could be generated from the measurements which do not follow the recommended guidelines (Fahey, Murphy and Hart, 2004). The importance of accurate and reliable BP measurement cannot be over emphasized (Mulrow, 2001; MacGregor and Kaplan, 2006).

Firstly, it could systematically prevent BP overestimation, and reduce the number of patients who inappropriately receive unnecessary treatment.

Secondly, it halts BP underestimation that denies access to essential treatment.

Thirdly, it could reduce the incidence of alleviated cardiovascular situations in people with high BP.

Fourthly, routine and accurate BP measurement helps in early prediction, prevention and treatment of high BP related diseases, including heart disease, kidney failure and stroke which have been shown to be global leading factors to death and disability. Accurate, reliable and routine BP measurement could ultimately reduce health cost for the society.

To achieve accurate BP measurement, several international organisations including the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNCDETHP) (1980), World Health Organization (WHO), International Society of Hypertension (ISH) (1993;1999), British Hypertension Society (BHS) (1999), European Society of Hypertension (ESH) (2003), American Heart Association (AHA) (2005), European Society of Cardiology (ESC) (2015), European Respiratory Society (ERS) (2015) and Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, and Assessment (2016) have produced recommended guidelines (Shapiro, et al., 1996; ACOG Committee on Obstetric Practice, 2002; Lemogoum, et al., 2003; O'Brien, et al., 2005; Pickering, et al., 2005; Krause, et al., 2011; Sharman, et al., 2016).

As recommended, the key points to achieve accurate BP measurement include:

- 1) Caffeine, smoking, and exercise to be avoided before BP measurement;
- 2) Subjects to be seated calmly for five minutes in a quiet environment before start of BP measurement;

- 3) Arm position should be placed at heart level with arm or leg uncrossed;
- 4) Correct cuff and bladder size should be used. A cuff with bladder should encircle at least 80% of the arm, with lower edge to be at least 2cm above elbow joint;
- 5) Cuff inflation should be at least 30mmHg higher than the point when there is no blood flow. Deflation should be steadily until the appearance of blood flow, at 2 to 3 mmHg per second;
- 6) If the korotkoff sounds are weak, subjects are recommended to raise the arm, open and close the hand from between five and ten times;
- 7) If the first two readings are significantly different by more than 5mmHg, averaged value from two or more readings separated by 2 minutes should be used (Pickering, et al., 2005);
- 8) BP readings should be recorded at the nearest 2 mmHg;

## 1.5 BP measurement techniques

As shown in figure 1.5, there are two main BP measurement techniques: invasive and non-invasive techniques.

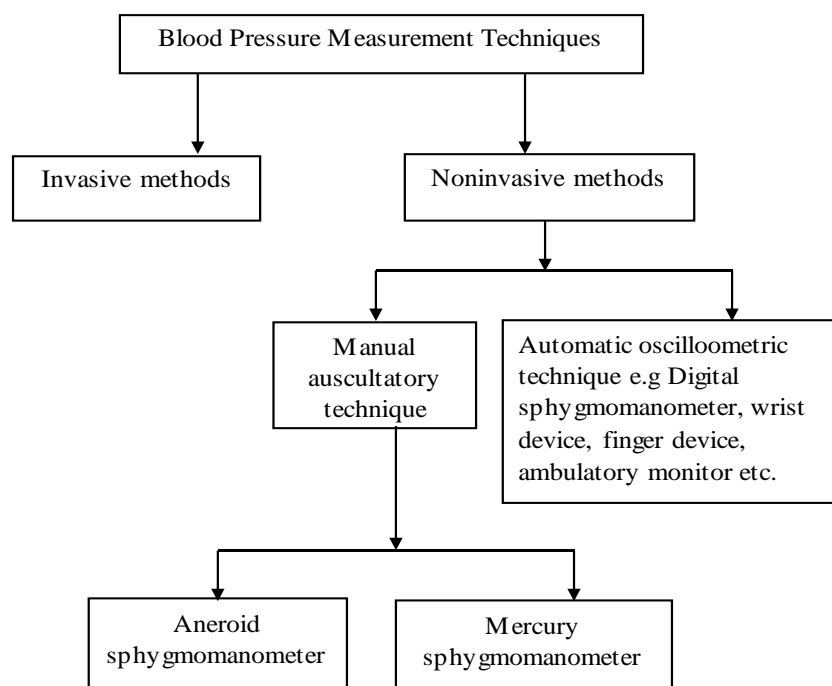


Figure 1.5: Diagram of BP measurement techniques.

### a) Invasive technique

The history of invasive BP measurement technique has been discussed in section 1.1. Although invasive BP measurement in clinical setting has its disadvantages, it is still the most accurate technique as it measure BPs directly in the arteries as shown in figure 1.6. The pressure bag is regulated by the pressure transducer and automatic flushing system and BP waveform is being displayed (Flaherty, Sher, and Caro, 2005). The disadvantages of invasive BP measurement technique include: it could be very painful and could cause blood bleeding from patients; it could lead to body exposure to some infectious diseases; and it requires a skillful and experienced person to operate. However, it has the advantage of displaying beat-by-beat BP waveforms and gives direct and more accurate BP readings especially in people with low BP (Shapiro, et al., 1996; Unit, 2001).

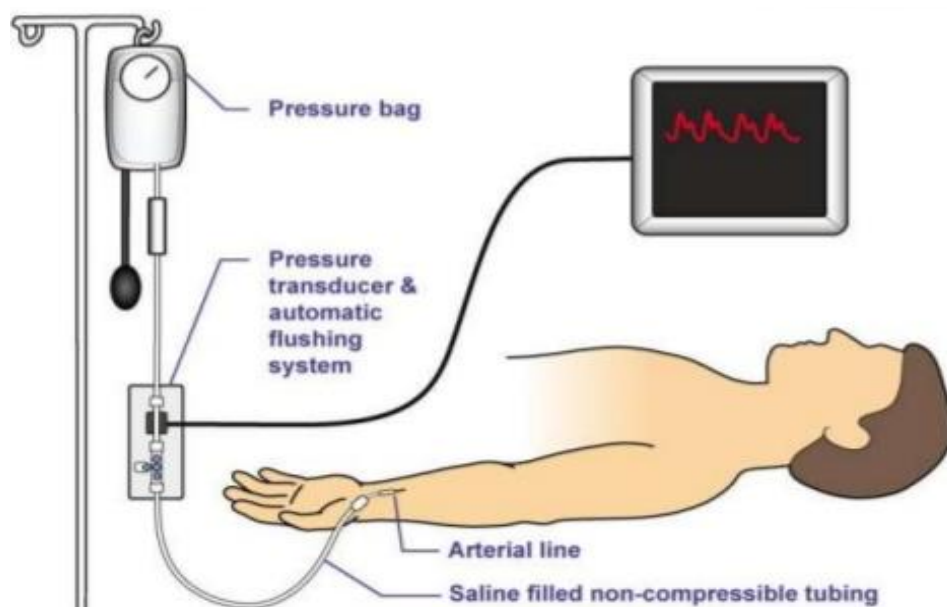


Figure 1.6: Invasive BP measurement technique.

### b) Non-invasive technique

Non-invasive technique is an indirect way to measure BP. Currently, there are two commonly used non-invasive techniques of measuring BP: **manual auscultatory technique** and **automatic oscillometric technique**.

In general, the advantages of non-invasive BP measurement include the fact that they are normally used for routine examination and monitoring. It is not painful to patients. Also, patients are not exposed to diseases and the risk of excessive blood lost. It is affordable and transportable. (Pickering, et al., 2005; Filipovský, et al., 2016).

## **1.6 Manual auscultatory technique**

In 1896, Scipione Riva-Rocci, an Italian physician, developed the manual BP measurement technique using an occlusive cuff in form of air filled bladder. It is today known as sphygmomanometer. Non-invasive manual BP measurement is achieved by wrapping a non-distensible cuff around the arm, which is inflated until the cuff pressure is above the brachial artery pressure to block blood flow. The cuff pressure is then released slowly, to the point when blood flow emerges back in the artery. As deflation continues, blood continues to flow until when there is full blood flow. The pressure at the point when blood first starts to flow back into brachial artery is the maximum arterial pressure, known as SBP. DBP is the minimum arterial pressure at which blood flow is fully restored back to the artery (FitzGerald and Drumm, 1977; Shapiro, et al., 1996; Benmira, et al., 2016).

In 1905, Nicolai Korotkoff, a Russian physician working at Imperial Medical Academy in St. Petersburg, used a stethoscope placed over the brachial artery to detect the sounds of the arterial pulses during the deflation of pressure in the cuff. The first whooshing sound heard is established to be first korotkoff sound which determines SBP. With further cuff pressure deflation, the artery opens and closes, causing more turbulent blood flow and further sounds to be heard. The last sound heard before complete disappearance of the sounds determine DBP. The sound disappears when the artery opens fully to allow smooth blood flow (FitzGerald and Drumm, 1977; Shapiro, et al., 1996; Imai, et al., 1989; Benmira, et al., 2016).

All the general advantages of non-invasive techniques apply to the manual auscultatory techniques. It is the gold standard clinical BP measurement. However, researchers still show dissatisfaction over the detection of korotkoff sounds (FitzGerald and Drumm, 1977; Shapiro, et al., 1996; Imai, et al., 1989; Benmira, et al., 2016). The main disadvantages of manual technique includes:

- 1) It cannot be used in a noisy environment;
- 2) Observations and readings may differ from observers;
- 3) It does not give accurate results in infants and hypotensive patients;
- 4) They cannot be performed by unqualified, unskilled and inexperienced operators;
- 5) Errors could be introduced due to improper cuff size, poor positioning, calibration or maintenance of manometer, body movement of patients and incorrect arm positioning in relation to heart (Imai, et al., 1989; Benmira, et al., 2016).

Nowadays, manual auscultatory technique includes: **mercury sphygmomanometer** and **aneroid sphygmomanometer**.

**a) Mercury sphygmomanometer**

Mercury sphygmomanometer, as shown in figure 1.7, consists of a manometer, an inflatable cuff bladder, a tube for pressure inflation-deflation and a stethoscope. The mercury manometer measures BP by observing height of mercury column on the display. The mercury column is used as simple gravity-based unit, characterized by millimeters of mercury (mmHg), which has become universally accepted units for recording BPs. Mercury sphygmomanometer has achieved the longest use for non-invasive BP measurement. However, the use of mercury sphygmomanometer is being debatable due to toxicity of mercury to the environment (O'Brien et al., 2003; Fahey, Murphy and Hart, 2004; Zheng, et al., 2011). European Standard recommends that mercury sphygmomanometers should display a warning of carefulness and caution

during usage. The International Standard Organization (ISO) instructs that mercury manometer should incorporate a stopping device at the top of the tube to prevent the spillage of liquid mercury. They also recommend that mercury reservoir should be fitted with stopping device to prevent mercury from flowing into the attached tube (Imholz, et al., 1990; Unit, 2001; Benmira, et al., 2016).

The major disadvantages of mercury sphygmomanometer as pointed earlier lies in the usage of mercury. Mercury spillage when inhaled can cause nausea, shortness of breath, pneumonitis and bronchitis. Long term exposure can lead to memory loss, stupor and coma. More seriously, when mercury is converted to methyl-mercury by microorganisms, it becomes dangerous to fetuses and young children. In addition, air leakage, and obstruction in the cuff could also introduce mechanical errors into the device (Unit, 2001; Filipovský, et al., 2016). Therefore, these environment concerns have led to the imposition of bans in some European countries and supply in the UK is now restricted to healthcare use (Fahey, et al. 2004).



Fig 1.7: Mercury Sphygmomanometer (Fahey, et al. 2004).

**b) Aneroid sphygmomanometer**

In comparison with mercury sphygmomanometers, the reading gauges are generally smaller. Aneroid sphygmomanometers has disadvantage of inaccuracy in BP measurement due to mechanical jolts. Another disadvantage is that the device could be damaged without notice (Fahey, Murphy and Hart, 2004).



Figure 1.8: Aneroid Sphygmomanometer (Fahey, Murphy and Hart, 2004).

**1.7 Automatic oscillometric technique**

Automatic oscillometric technique was originally established by Marey in 1876 (Pickering, et al., 2005). It operates with the principle of amplitude oscillations of pressure in the cuff. During cuff inflation, each heart beat produces an oscillation in blood vessels, which corresponds to the amplitude of the cuff pressure oscillations. With this technique, BPs are determined indirectly via empirical derived algorithms and displayed electronically Figure 1.9 shows the oscillometric waveform extracted from the deflating cuff pressure (bottom trace) and the oscillometric characteristic ratios for SBP, Mean Arterial Pressure (MAP) and DBP determination. MAP is determined at maximum point of the amplitude, SBP and DBP are estimated by the characteristic ratios of 0.5 and 0.7 respectively (Pickering, et al., 2005; Benmira, et al., 2016).



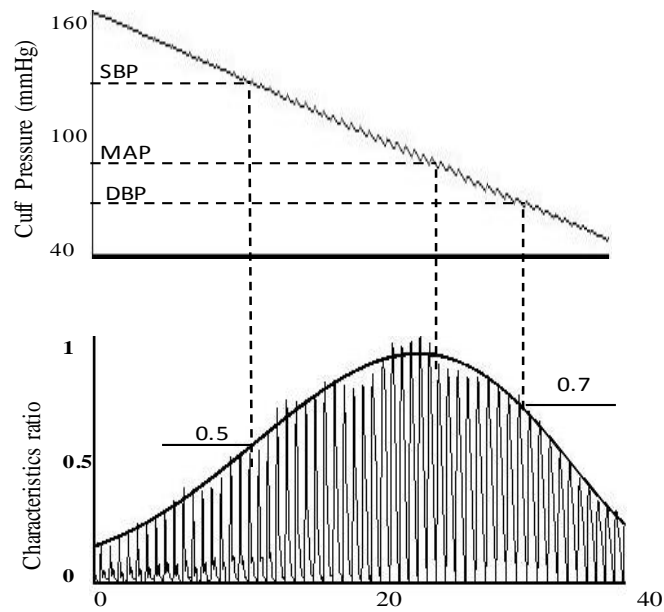


Figure 1.9: Illustration of automated BP determination method (adopted from Benmira, et al., 2016).

The majority of automated/digital BP devices, as shown in figure 1.10, operate with oscillometric technique. They operate with manual or electronic pump to introduce pressure to the cuff and do not need stethoscope to detect the korotkoff sounds. (Pickering, et al., 2005).



Figure 1.10: Automatic/digital BP devices (Pickering, et al., 2005).

Today, the uses of automated BP devices are increasing because individuals are being encouraged to buy their own devices for self-monitoring of BP at home and offices. The 24-hour ambulatory BP monitors also operate with the principle of oscillometric technique. Other automatic BP devices include wearable wrist BP device with an electrically driven pump attached to a wrist cuff, and the continuous non-invasive BP

measurement device with a sensor attached to the fingertip that operates with the arterial pulse wave analysis methods (O' Brien, et al., 2005; Pickering, et al., 2005; Gorostidi, et al., 2016; Hamdani, et al., 2016; Isiguzo, et al., 2016).

It has been widely known that readings obtained from clinically validated automated devices are accepted. The advantages of automatic oscillometric technique include:

- 1) It is easy to use;
- 2) It has no observer bias;
- 3) It is mercury free;
- 4) It can be used in a noisy environment.

The inconsistency of BP measurement by automatic oscillometric device has been reported by Park, Menard and Yuan (2001). The disadvantages are as follows:

- 1) They are very sensitive to patient movement and the automatic BP calculation algorithm based on characteristics ratio may not work accurately with motion artifact.
- 2) It may produce inaccurate reading in patients with heart and circulation problems such as arteriosclerosis, arrhythmia, preeclampsia etc.

Before the automated BP devices could be sold in the market, they need pass the requirement of International Standard Organisation (ISO) with clinical trials. Automatic BP device are normally validated under resting condition. However, for clinical research purpose these automatic BP devices are commonly used under non-resting condition. Unfortunately, automatic oscillometric BP devices are not yet validated for BP measurement under non-resting conditions. The readings from these non-resting measurement are therefore questionable and should be carefully interrupted.

## **CHAPTER 2      Pregnancy Induced Hypertension (PIH) and its management**

The chapter gives a general overview of pregnancy induced hypertension (PIH), including its definition, classification, development, symptoms and diagnosis. It also reviews existing strategies on PIH management. Finally, the aim and objectives of this research work, with the organization of this thesis work, are outlined.

### **2.1      General overview of PIH**

Pregnancy is the period a woman carries a fertilized egg inside her uterus until when the baby is born. Pregnancy period (normally 40 weeks) is known as gestation or conception period (Fleischman, Oinuma and Clark, 2010; Medical dictionary, 2011; Venes, 2013). The whole pregnancy period is divided into three trimesters which is made up of three months each. The first trimester is a period in which the embryo develops, the second trimester is a period in which the embryo turns into a foetus, and the third trimester is a period in which the foetus gains weight and gets ready for delivery (Llewellyn-Jones, 1972; Magowan, Owen and Thomson, 2014).

There are many factors affecting pregnancy, including hypertension, diabetes, risk of premature rupture of membrane, preterm labour, infant respiratory distress syndrome, genital track abnormalities, excess amniotic fluid, deficient of amniotic fluid, sexually transmitted diseases, etc. Among them, hypertension is one of the most significant threats for both the life of mother and fetus during pregnancy (Chesley, 1978; Teklu and Gaym, 2006; Amro, et al., 2015). As reported by McGillivray et al., (1980), hypertension is the second leading cause of neonatal and maternal morbidity and mortality (Arulkumaram and Lightstone, 2013).

### 2.1.1 Definition of PIH and its classification

A generally accepted definition of hypertension during pregnancy is still lacking. It is usually linked to BP increase during gestational period (Kintiraki, et al., 2015), but it should be noted that lots of definitions have been used based on the classification and diagnosis of high BP during pregnancy. Calder (1992) suggested that hypertension during gestational period should be referred to as PIH. Today, PIH appears to be commonly accepted term to describe high BP during pregnancy. Drife and Magowan (2004) stated that PIH is a multisystem disorder and has the possibility of affecting every organ of a pregnant woman, especially the liver, lungs, kidney, brain cardiovascular systems, etc.

The classification of PIH has been a major concern in health care community among individuals and group researchers. There has been some agreement among different researchers over the PIH classification, as shown in table 2.1.

Table 2.1: Classification of PIH			
S/N	PIH	Its significance	Start period in gestation
1	Gestational hypertension:	Hypertension without significant proteinuria	After 20 weeks but disappears within 10 days after delivery
2	Pre-eclampsia:	Hypertension with significant proteinuria	After 20 weeks
3	Chronic hypertension:	Present at the booking visit and already taking antihypertensive medication	Before 20 weeks
4	Eclampsia:	Pre-eclampsia with convulsion	Prolonged pre-eclampsia
(Calder and Dunlop, 1992; Davey and MacGillivray, 1988; National High Blood Pressure Education Program, 2000; Australasian Society for the Study of Hypertension in Pregnancy (ASSHP), 2001; Brown, et al., 2001; Zamorski and Green, 2001; American College of Obstetricians and Gynaecologists 2002; James, et al., 2010; NICE Guideline 107, 2010; Haines, Macnab and Raajkumar, 2013; Symonds, Symonds and Arulkumaran, 2013 and Suzuki, et al., 2015).			

### 2.1.2 Development of PIH

The underlying physiological causes of PIH are still debatable. The American College of Obstetricians and Gynaecologists (ACOG) 2002 reported that PIH occurs with high

BP but manifests after twenty week of pregnancy (Symonds, Symonds and Arulkumaran, 2013). Contrarily, the Australian Society for the Study of Hypertension in Pregnancy (ASSHP), National High Blood Pressure Education Program (NHBPEP), World Health Organisation (WHO) and Canadian Hypertension Society (CHS) suggest that the diagnosis of hypertension and the presence of protein in urine are the major symptoms of PIH during pregnancy.

The development of PIH is presented in figure 2.1. As shown, preeclampsia starts to develop and can be diagnosed before the fourth week of pregnancy (first trimester). If left untreated, the symptoms (see figure 2.2) will start manifesting from the twentieth week in the second trimester. Untreated preeclampsia leads to eclampsia. When eclampsia sets in, it could lead to early delivery of the baby at the third trimester (Sibai, 1990; Duckitt and Harrington, 2005; Shennan, 2016; Rolleston and Camb, 2007). NICE clinical guideline (2015) states that normal BP should be below 140 mmHg during pregnancy. However, the normal BP values at the three different trimesters of pregnancy have not been specified.

### 2.1.3 Symptoms and signs of PIH

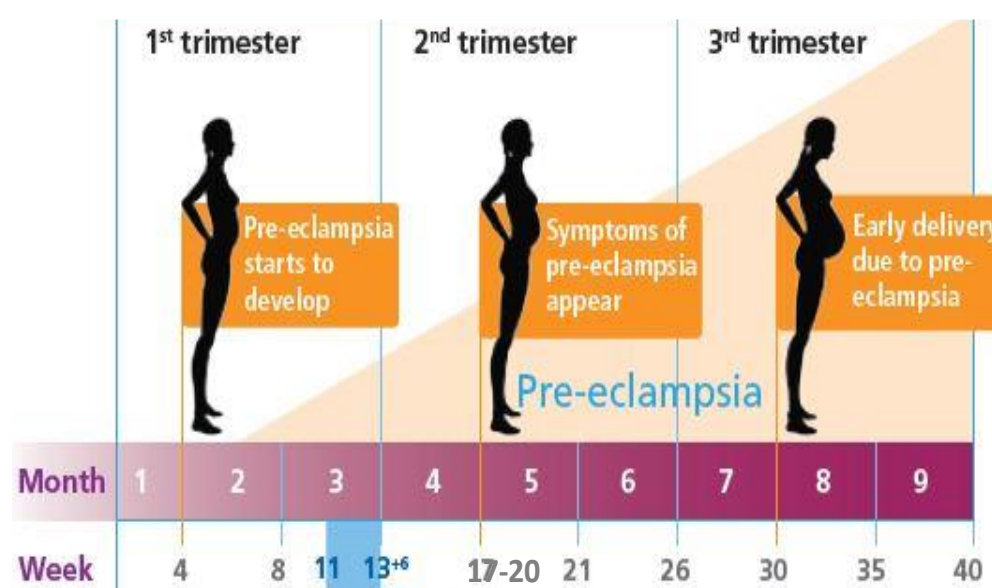


Figure 2.1: Development of preeclampsia during pregnancy (Earlybirds, 2015).

Symptoms and signs of PIH are the subjective and visible evidences or feelings experienced by a pregnant women at early stage of PIH. It could be noticed by doctors, nurses, family members, neighbours and sometimes friends. Figure 2.2 and table 2.2 show the common symptoms and signs of PIH (Calder, Dunlop and Dunlop, 1992; Villar, et al., 2006; Kenny, et al., 2010; Maputle, Khoza and Lebese, 2015).

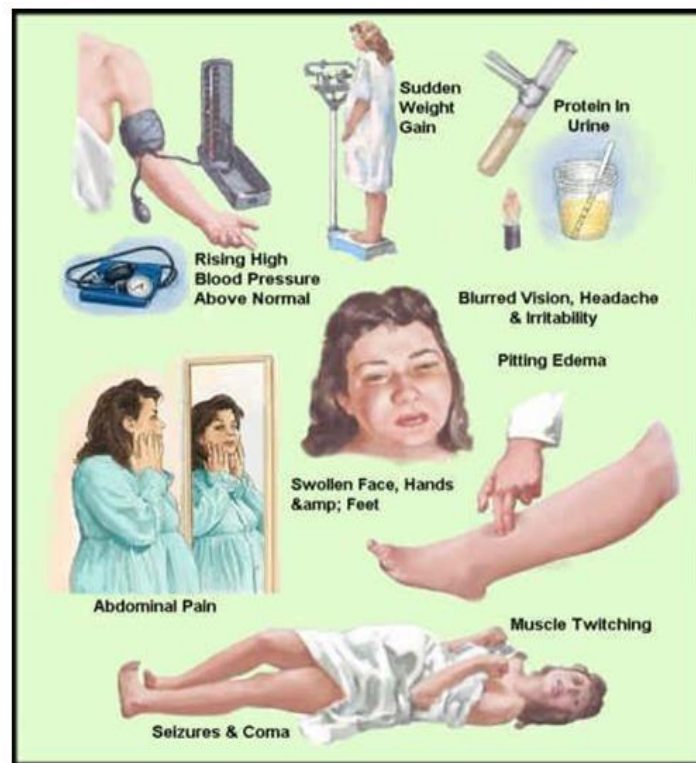


Figure 2.2: Typical signs and symptoms of PIH (Villar, et al., 2006; Benrubi, 2012).

Long persistent signs and symptoms of PIH could eventually lead to the followings:

- 1) Placental abruption: This could cause abnormal and premature separation of placenta from the inner lining of the uterus;
- 2) Low birth weight babies: This is due to decrease in blood supply to the placenta.
- 3) Cardiovascular diseases and respiratory distress may occur;
- 4) HELLP syndrome: HELLP means Hemolysis Elevated Liver enzymes and Low Platelet count. This may occur even before high BP is detected and could be fatal for both mother and baby, resulting in damaged organ;
- 5) Death: If convulsion occurs, it could lead to coma and death of mother and child.

Table 2.2: Signs and symptoms of PIH

Signs		Symptoms		
1	Oedema of face, hands and feet	1	Proteinuria	
2	Sudden weight gain	2	Abdominal pain, Lower back pain	
3	Restlessness, agitation, dizziness and drowsiness	3	Headache, Fever	
4	Vomiting of blood	4	Blurred vision	
5	Retinal oedema	5	High blood pressure	
		6	Inadequate functioning of the liver	
		7	Low platelet level in blood	
		8	Ringing or buzzing sound in the ear	
		9	Hyperreflexia	
		8	Breathing difficulty	
(Modified from Calder, Dunlop and Dunlop, 1992; Villar, et al., 2006; Kenny, et al., 2010; Maputle, Khoza and Lebesse, 2015)				

#### **2.1.4 Epidemiology of PIH**

According to Osungbade and Ige (2011), PIH has affected between 2 to 10 percent of pregnancies globally. WHO has estimated that this health disorder occurs more in developing countries than in developed countries (Omole-Ohonsi, et al., 2008; Kintiraki, et al., 2015). In developed countries such as North America and Europe, the case has been estimated to be between 5 to 7 percent. In African countries such as Nigeria, South Africa, Egypt, Tanzania and Ethiopia, its occurrence varies between 1.8 and 16.7 percent (Mahaba, et al., 2001; Thiam, et al., 2003; Kimbally, et al., 2007; Omole-Ohonsi, et al., 2008; Olopade and Lawoyin, 2008; Osungbade and Ige, 2014; Kintiraki, et al., 2015;). To be specific, Anorlu, Iwuala and Odum (2005) found that, one hundred and thirty seven (137) women out of one thousand eight hundred and three (1803) pregnant women were diagnosed of PIH in one tertiary hospital in Lagos State Nigeria, between February 2001 and August 2002. Gurrier, et al., (2013) recorded in Jahun Hospital, Nigeria, that about four hundred and nineteen (419) pregnant women are diagnosed of hypertension between October 2010 to May 2011. Xie, et al., (2013) reported eighteen thousand, one hundred and seventeen (18,117) women with PIH from their study in Saskatchewan hospital, from January, 1980 to December 2005.

#### **2.2 Diagnosis of PIH**

When the signs and symptoms of PIH occur, diagnostic tests should be undertaken to confirm the health disorder in pregnant women. Some of these diagnostic tests are direct while the others are indirect. They are summarized in Table 2.3.

#### **2.3 Management of PIH**

PIH management involves early education about general lifestyle and nutrition during pregnancy. Education on warning symptoms is also very vital and should be given during antenatal visits. Several international societies including Joint National



Committee (JNC) on Hypertension, American Diabetes Associate (ADA), American Heart Association/American and Stroke Association (AHA/ASA), European Society of Hypertension (ESH), European Society of Cardiology (ESC) and World Health Organisation (WHO) have recommended measures and lifestyles to prevent PIH which include (Craici, Wagner and Garovic, 2008; Facchinetti, et al., 2009): Reduction of salt intake; taking of at least eight glasses of water a day; adequate intake of protein; fruits and vegetables; adequate intake of routine drugs; adequate exercising and rest.

Proper management at early stage could avoid further complications such as convulsions, cerebrovascular haemorrhage, pulmonary oedema, renal failure, abruption placenta, foetal death, leading to a healthy delivery of a child with minimal trauma to the pregnant mother (Evans, 1989; James, et al., 2010).

However, if signs and symptoms of PIH have manifested, Sibia (2003) suggested that its management strategies should depend on the severity, period and nature of the PIH. The other factors to be considered include the foetal gestation age and its status. Consequently, PIH during pregnancy has created a lot of concerns to mothers, families, clinicians, nurses, etc. (Khalil, Jauniaux and Harrington, 2009), and has generated big challenges over PIH management. This eventually affects societal life and will reduce maternal and perinatal morbidity and mortality. No wonder a lot of studies have been reported on how to effectively manage PIH. (Khalil, Jauniaux and Harrington, 2009; Okafor, et al., 2009; Roberge, et al., 2012; Enaruna, Aziken and Cert, 2014). Table 2.4 provides a brief summary of management of PIH.

.

Table 2.3: Summary of diagnostic tests of PIH

	Direct diagnosis	Result	Indirect diagnosis	Result
1	Blood pressure measurement	> 140/90 mmHg	Proteinuria test	> 5g per 24hrs
2	Weight measurement	> 3.6kg after 20 <sup>th</sup> week	Doppler ultrasonography	Presence of high resistance index/early diastolic notch
3	Assessment of oedema	Present	Chest radiography	Presence of pulmonary oedema
4			Magnetic resonance imaging	Presence of abnormalities in cerebral cortex and foetal tumours
5			Biomarkers	Increase or decrease of maternal serum concentration depending on biomarker
6			Oliguria	< 400 ml in 24 hrs

(Thomson, Hytten and Billewicz, 1967; FitzGerald, et al., 1977; Chesley, 1978; Macgillivray and Campbell, 1980; O' Brien, et al., 2003; Magee, et al., 2008, 2014; Carty, et al., 2008; Kenny, et al., 2010; Visintin, et al., 2010; Kuc, et al., 2011; Ogoole, et al., 2012; Gray, et al., 2013; Evans, et al., 2013; Moore Simas, et al., 2014; Syed and Ramanappa, 2014; Anderson, et al., 2015; Ayyuba, Abubakar and Yassi, 2015 Foo, et al., 2015; Hartwig, 2015; Mehra et al 2015; Hartwig 2015, Wu, et al., 2015; Schenone, et al., 2015 and Ter Haar, et al., 2015)

Table 2.4: Management of PIH

Management	PIH		
	Gestational hypertension	Preeclampsia	Chronic hypertension
1 <i>Admit to Hospital</i>	No	Yes	Yes, until BP < 159/109mmHg
2 <i>Treat</i>	No	No	Apply as 1 <sup>st</sup> line Oral Labetalol to keep DBP= 80-100 & SBP= $\leq$ 150
3 <i>Measure BP</i>	Once or twice a week	At least 4 times a day	At least 4 times a day
4 <i>Test of proteinuria</i>	At each visit using automated reagent strip reading device or urinary protein:creatinine ratio	Do not repeat quantification of proteinuria	Daily using automated reagent strip reading device or urinary protein: creatinine ratio
5 <i>Blood test</i>	For routine antenatal care. Test kidney function electrolyte, full blood count transaminases, bilirubin if necessary.	Monitor twice a week with the following test: kidney function, electrolytes, full blood count transaminases, bilirubin.	Test and then monitor weekly: Test kidney function, electrolytes, full blood count transaminases, bilirubin
6 <i>Gestational age greater than 37 weeks</i>	Delivery at 37 week if BP < 160/110 without anti hypertensive drug	Delivery between 34 to 37 weeks depending on maternal/ foetal condition	Delivery at 37 week if BP < 160/110 without anti hypertensive drug

(Modified from Sibai 2003; Sibai and Stella, 2009; Haines, Macnab and Rajkumar, 2013; Xie, et al., 2013)

## **2.4 Pharmacological treatment of PIH**

The Japanese Society of Hypertension (JSH) and Japanese Society for the study of Hypertension in Pregnancy published a guideline for basic pharmacological treatment of PIH. The antihypertensive drugs that could be taken is summarized in table 2.5.

This is in agreement with the guideline of American College of Obstetricians and Gynecologists Committee (2002). These major guidelines (Podymow and August, 2008; 2011, Arulkumaran and Lightstone, 2013; Xie, et al., 2013; Suzuki et al., 2015; Vadhera and Simon, 2015; Pucci, et al., 2015) consider the severity of PIH with intention of lowering its escalation during treatment.

## **2.5 Non-pharmacological treatment of PIH using respiratory exercise**

Until now, existing pharmacological approaches have done well in treating PIH, although some studies have shown concerns of antihypertensive drugs taken during pregnancy, which are outlined in table 2.5. It is shown that, on average, antihypertensive drugs like monodrug therapy with ACE inhibitors could reduce SBP and DBP respectively by 12.5 and 9.5 mmHg, alpha1-blockers by 14.8 and 12.2 mmHg, calcium channel blockers by 15.3 and 10.5 mmHg, and thiazide and loop diuretics could reduce SBP by 15.3 and 15.8 mmHg respectively and DBP by 9.8 and 8.2 mmHg respectively (Wu, et al., 2005).

Notwithstanding, there have been some suggestions for an alternative treatment of hypertension by respiratory exercise (Kim, 1994; Mason, et al., 2013; Pattanshetty and Thapa, 2015; Tomicic, et al., 2015; Hamdani, et al., 2016). Many studies, as seen in table 2.6a, have shown that deep breathing can reduce BP for normal and non-pregnant hypertensive subjects, which was re-grouped in Table 2.6b depending on the BP techniques employed and the type of subjects recruited, indicating the possibility of introducing non-drug treatment of PIH.

Table 2.5: Antihypertensive drugs on pregnancy.

		Benefits	Concerns (possible effect on pregnant mother)
1	<b>Antihypertensive Drugs</b> Methyldopa (preferred)	Proven safety and efficacy	Depression, hepatic disturbances, haemolytic anaemia may not lower BP adequately
	Clonidine (alternative)	Proven safety and efficacy	Limited data regarding foetal safety
2	<b>Beta Blockers</b> Labetalol (alpha and beta blocking agent (preferred)	Safety (similar to methyldopa and may be more efficacious than methyldopa	Larger doses can cause neonatal hypoglycaemia
	Atenolol (contraindicated)	Not Applicable	IUGR (Intra Uterine Growth Restriction)
3	<b>Calcium Channel Blockers</b> Verapamil (alternative)	Efficacy and similar to other oral agent	Risk of interaction with magnesium (can cause bradycardia)
4	<b>Direct Vasodilators</b> Hydralazine (preferred)	Efficacious intravenous agent. European Society of Hypertension(ESH) no longer recommends it	Maternal polyneuropathy, tachycardia, drug-induced lupus, neonatal lupus and thrombocytopenia, tachyphylaxis
	Nitroprusside (alternative)	Only considered for life- threatening severe hypertension	Cyanide and thiocyanate toxicity, must be carefully monitored. There is risk of cardio-neurogenic syncope
5	<b>Diuretics</b> Thiazide	Useful in chronic hypertension	Volume contraction, electrolyte abnormalities – rare with small doses
	Spirolactone (contraindicated)	None	Possible foetal anti-androgen effects

(Modified from Schachter, 2002; Podymow and August, 2008; Khali, et al., 2009; Magee, et al 2014)

Table 2.6a: Past studies on effect of deep breathing on blood pressure (2001-2016)

	Author(s)	Study type	No of Subjects ( N/H)		BP Device employed		BP Decrease (mmHg)		
			Normal (N)	Hypertensive (H)	Manual (M)	Auto (A)	SBP	MAP	DBP
1	Schein et al., (2001)	Randomized control trial	-	149	M	-	15.2	10.0	11.7
2	Rosenthal et al., (2001)	Pre-post observational study	-	13	M	-	7.2	-	3.4
3	Grossman et al., (2001)	Prospective matched case-control	-	33	-	A	7.5	-	4.0
4	Grossman et al., (2001)	Prospective matched case-control	8	-	-	A	2.9	-	1.5
5	Jagomagi et al., (2003)	Randomized control trial	13	-	M	-	9.1	5.9	4.3
6	Viskoper et al., (2003)	Randomized control trial	-	17	-	A	12.9	-	6.9
7	Meles et al., (2004)	Prospective matched case-control	-	79	M	-	5.5	-	3.6
8	Elliot et al., (2004)	Randomized control trial	-	149	-	A	7.3	-	1.9
9	Augustovski et al., (2004)	Cross sectional study	-	73	M	-	10.9	-	5.4
10	Mori et al., (2005)	Randomized control trial	4377	3066 (untreated) 11,217 (treated)	Not available		6.4 9.6 8.3	- - -	2.3 3.0 2.8
11	Elliot and Izzo, (2006)	Case report	-	1	-	A	17	-	14
12	Parati and Carretta (2007)	Randomized single blind control	-	30	-	A	7.5	-	1.0
13	Parati and Carretta (2007)	Randomized single blind control	-	30	-	A	12.2	-	5.5
14	Mouya et al., (2009)	Randomized prospective control	-	60	-	A	-	-	-
15	Subramanian et al., (2011)	Randomized control trial		8	Not available		2.4	-	2.4
16	Zheng et al., (2012)	Randomized control trial	111	-	M	-	4.4	-	4.8
17	Ravi et al., (2015)	case-control study	30	-	-	A	Not available		
18	Mahani et al., (2016)	Randomized control trial	-	494	-	A	2.5	-	2.2
19	Drozdz et al., (2016)	Randomized control trial	-	40	Not available		20	-	10
20	Wolff et al., (2016)	Randomized control trial	-	96	Not available		3.8	-	1.7

**Table 2.6b: Past studies on effect of deep breathing showing BP technique employed and type of subjects recruited.**

	Author(s)	Type of subjects (N/H) <i>Normal (N) or Hypertensive (H)</i>	BP Device employed <i>Manual (M) or Automatic (A)</i>	BP reduction (mmHg)		
				<i>SBP</i>	<i>MAP</i>	<i>DBP</i>
1	Schein et al., (2001)	<i>Hypertensive (H)</i>	<i>Manual</i>	15.2	10.0	11.7
2	Rosenthal et al., (2001)			7.2	-	3.4
3	Augustovski et al., (2004)			10.9	-	5.4
4	Meles et al., (2004)			5.5	-	3.6
5	Jagomagi et al., (2003)	<i>Normal (N)</i>	<i>Manual</i>	9.1	5.9	4.3
6	Zheng et al., (2012)			4.4	-	4.8
7	Grossman et al., (2001)			2.9	-	1.5
8	Grossman et al., (2001)	<i>Hypertensive (H)</i>	<i>Automatic</i>	7.5	-	4.0
9	Viskoper et al., (2003)			12.9	-	6.9
10	Elliot et al., (2004)			7.3	-	1.9
11	Elliot and Izzo, (2006)			17	-	14
12	Parati and Carretta (2007)			7.5	-	1.0
13	Parati and Carretta (2007)			12.2	-	5.5
14	Mahtani et al., (2016)			2.5	-	2.2

## **2.6 Objectives of this research**

It has been reported that deep breathing could decrease manual auscultatory BPs on non-pregnant subjects. The automated BP decrease with deep breathing has also been reported with measurements taken from different automatic BP devices. Unfortunately, automatic devices have not been validated for the non- resting conditions, leading to a question on how confidence the results from these studies of investigating the effect of deep breathing using automatic devices could be. Moreover, there are no quantitative clinical data available on the effect of deep breathing on BPs measured by manual and automatic techniques simultaneously. This research aims to provide quantitative clinical data on the magnitude of simultaneous effect of deep breathing on both manual auscultatory and automated BPs.

Nevertheless, deep breathing could be potentially used for PIH management. However, to the best of my knowledge, there is no study providing evidence on PIH management using respiratory exercises. Before deep breathing can be widely adopted for PIH management, more solid scientific evidence is required. As a preliminary study, our investigation will also be performed on normal pregnant women. The outcome of this research could ultimately lead to the development of a device to guide breathing for PIH patients, and be a stepping stone to the final aim of management and treatment of PIH by respiratory exercise.

The main objectives of this study include:

- 1) To conduct a comprehensive literature review on BP measurements and PIH management including the effect of deep breathing on BPs;
- 2) To quantify the effect of regular deep breathing on manual auscultatory BP;
- 3) To quantify the effect of regular deep breathing on automated BP determined from oscillometric waveforms recorded during manual BP measurement, allowing the



comparison of simultaneous effect of regular deep breathing on both manual and automatic technique on normal healthy subjects;

- 4) To preliminary quantify the effect of deep breathing on normal pregnant women.

To achieve the above objectives, the following will be conducted:

- 1) **Understand the physiological measurements on normal healthy subjects and pregnant women:** This involves understanding of BP measurement principle and recommended measurement procedure on human subjects.
- 2) **Digital signal processing using MATLAB:** This will involve the automatic BP determination from the recorded deflating cuff pressure waveform.
- 3) **Data and statistical analysis:** This will involve the use of excel to record all the collected data and then transfer it to SPSS Statistics 17 software package (SPSS Inc., USA). SPSS will be used to perform analysis of variance (ANOVA) for the measurement repeatability and to investigate the effect of deep breathing on both manual and automated BPs. Bland-Altman will be used to illustrate the measurement repeatability and difference in BP changes with deep breathing.
- 4) **Data summary:** This will involve the comparison of BP changes with deep breathing measured by different techniques (manual and automatic) and BP difference between different breathing conditions (normal resting, during and after deep breathing)

## **2.7 Organization of this thesis**

**Chapter One** introduces a general overview of BP and its measurement techniques. The treatment of hypertension is also discussed with emphasis on non-pharmacological treatment using respiratory exercise.

**Chapter Two** gives a general overview of pregnancy induced hypertension (PIH), including its definition, classification, development symptoms and diagnosis. It also

reviews existing strategies on PIH management, the aim and objectives of this research work, and ends with the organization of this thesis work.

**Chapter Three** gives the key methodologies for two studies on normal healthy subjects and pregnant women, including the measurement procedure, data collection, and statistical data analysis.

**Chapter Four** summaries the results of the simultaneous effect of regular deep breathing on manual and automated BPs, and the comparisons between the changes on both manual and automatic BPs. Finally, the effect of deep breathing on automated BP from pregnant women is also reported.

**Chapter five**, is the final chapter. It discusses the conclusion, some challenges faced during the study and recommendations for future work.

## **CHAPTER 3 Methodology and data analysis**

This chapter explains the measurement protocols and data analysis for two experimental studies involved in this research work. Study 1 is for the simultaneous effect of deep breathing on BPs measured by manual and automatic techniques on normal healthy subjects. Study 2 is for the effect of deep breathing on automated BPs using pregnant subjects, aiming to provide evidence on whether deep breathing can be served for non-pharmacological management to PIH.

### **3.1 Study 1: Simultaneous effect of deep breathing on manual and automated BPs**

#### **3.1.1 Subjects**

Thirty-nine (39) healthy normal subjects (24 male and 15 female; 18 to 75 years old) without known cardiovascular diseases were recruited to participate in this study. Any subjects with known history of cardiovascular diseases were excluded from the study. The data collection was done by the research team from Newcastle University, London. An ethical permission was received from the Newcastle & North Tyneside Research Ethics Committee. Anonymized data was analyzed. The investigation conformed to the Declaration of Helsinki, and all subjects gave their written informed consent to participate in the study.

#### **3.1.2 Preparation before BP measurement on normal healthy subjects**

The manual BP measurements were operated by a trained observer. Before the manual BP measurement, each subject was asked to seat in a chair comfortably with feet placed on the floor. The arm was supported at heart level. Each subject was given a 5 minutes to rest for cardiovascular relaxation. Other preparations include:

- 1) Each subject fills in and signs a consent form to participate in the study and to confirm that they have no known history of cardiovascular diseases;

- 2) Measure the arm circumference using a tape to determine the cuff size;
- 3) A data collection form was designed to record the name, address, age, gender, arm circumference and BPs obtained during manual auscultatory measurement.

### **3.1.3 Measurement environment**

All the measurements in this study were undertaken in a temperature controlled room at  $26 \pm 1$  °C. The window blinds were well covered to block the sunlight and the ceiling lights were switched on. The room was kept tidy and quiet to make subjects feel comfortable during the measurement and to limit disturbances. No distraction was allowed from the operator during the whole measurement.

### **3.1.4 Measurement protocol and procedure**

Figure 3.1 shows the measurement protocol. During manual BP measurement, the oscillometric cuff pressure was recorded from the cuff to a computer to determine automated BPs (SBP, MAP and DBP) while manual BPs (SBP, MAP and DBP) were measured by a trained and experienced observer using manual auscultatory technique. The same observer was used during the whole experiment. This details are given in the schematic diagram of the measurement system, as shown in figure 3.2.

Figure 3.3 shows the BP measurement protocol. For each subject, two BP measurements were performed under resting and deep breathing conditions. To ensure slow and deep breathing pattern was consistent between subjects, a guided respiratory waveform (5 s inhalation and 5 s exhalation) was displayed on a computer screen for each subject to follow. The order of the two measurement conditions was randomized between subjects. They were then repeated three times giving a total of six BP measurements. A time interval of at least 4 minutes was given between repeat sessions, and at least 1 minute between the two BP measurements within a session, allowing the recovery of cardiovascular hemodynamic. The first measurement session was used to

introduce the subjects to the measurement protocol. A total of 156 BP measurements (from 39 subjects x 2 conditions x 2 repeats) were used for further analysis from all the subjects.

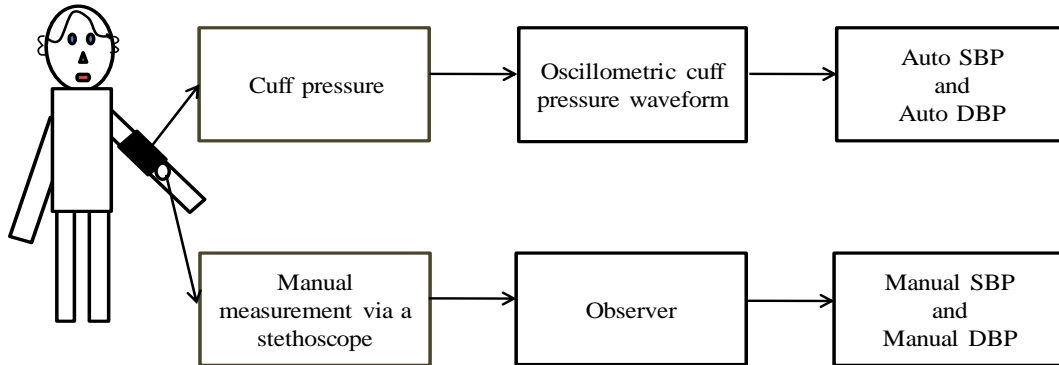


Figure 3.1: Block diagram of measurement system of study 1.

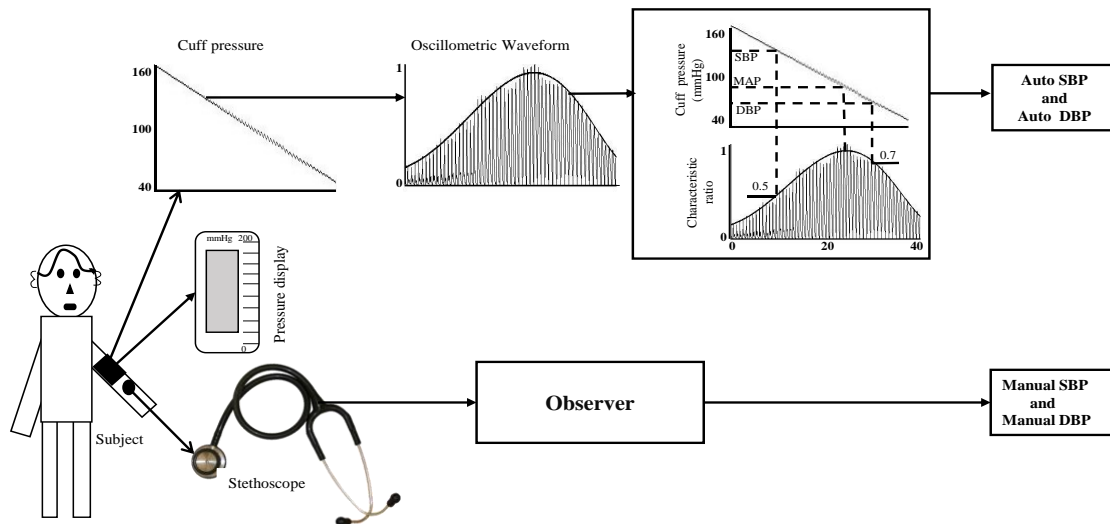


Figure 3.2: Schematic diagram of measurement system of study 1. Manual systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained through manual auscultatory technique by an observer. The oscillometric cuff pressure waveform was used to estimate automated SBP and DBP.

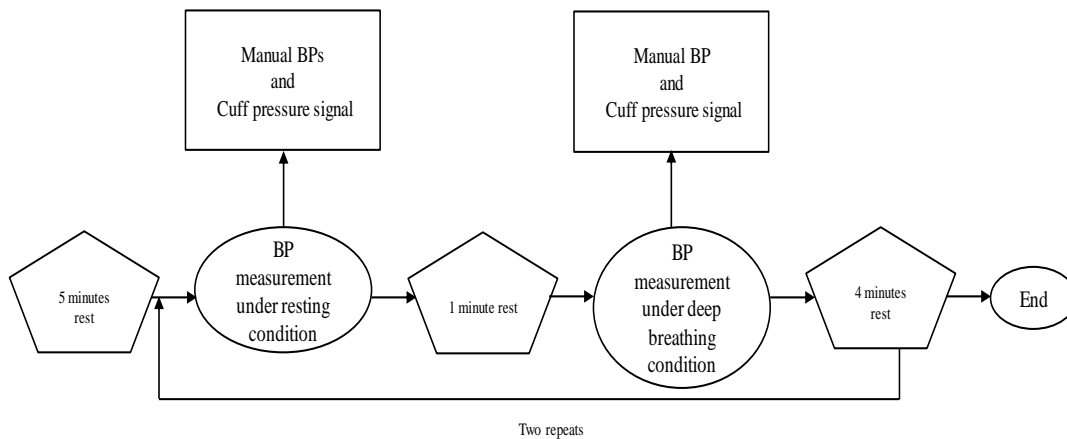


Figure 3.3: BP measurement protocol of study 1. During deep breathing condition, the subjects performed deep and slow breathing for about 1 min. During this period, the BP measurement was undertaken.

### **3.1.5 BP Determination**

#### **a) Manual auscultatory BP measurement**

A clinically validated manual electronic sphygmomanometer [Accoson Greenlight 300; AC Cossor & Son (Surgical) Ltd, Harlow, UK (Graves et al., 2003) was employed as pressure display to conduct all the manual auscultatory BP measurements. Manual auscultatory BP was measured by a trained and experienced operator under standard cuff deflation rate of 2-3mmHg/s. The same operator was used during this study. The manual SBP and DBP were determined from the appearance and disappearance of the korotkoff sounds, respectively. Manual MAP was estimated from the manual DBP plus one third of the absolute difference between SBP and DBP.

#### **b) Automated oscillometric BP measurement**

The oscillometric cuff pressure were digitally recorded to a computer for offline oscillometric waveform analysis as the cuff pressure was deflated at 2-3mmHg/s. A fast sampling rate of 2000Hz was used due to the frequency feature of korotkoff sounds. Automated SBP, MAP and DBP were determined from the recorded cuff pressure using an interactive software developed with Matlab 7.1 (MathWorks Inc. Natick, Massachusetts USA). A 6<sup>th</sup> order polynomial curve was used to fit to the sequence of oscillometric pulse peaks. As shown in figure 3.2, automated SBP, MAP and DBP were determined from the cuff pressure corresponding to 0.5, 1.0 and 0.7 respectively of the modelled envelope, with SBP lay above MAP and DBP lay below MAP.

### **3.1.6 Data analysis and statistical analysis**

Figure 3.4 shows schematic diagram of data analysis procedure for study 1. BP data obtained from both manual auscultatory and automatic oscillometric techniques were compared under resting and deep breathing conditions. The mean and standard deviation (SD) of both manual and automated BPs (SBP, DBP and MAP) across all

subjects were calculated separately for resting and deep breathing conditions using Excel. The Statistical Package for the Social Science (SPSS) Statistics 17 software package (SPSS Inc., USA) was employed to perform Analysis of Variables (ANOVA) for the measurement repeatability and the effect of deep breathing on both manual and automated BPs.

BP changes with deep breathing were calculated for each subject, separately for SBP, MAP and DBP, and for both manual auscultatory and automatic oscillometric techniques. The mean BP change with deep breathing and standard error mean (SEM) of their changes were obtained across all the subjects. P-value was calculated from within-subject paired changes using one way ANOVA with repeated measures, and a p-value below 0.05 was considered statistically significant. Finally, the percentage of subjects with BP reduction in both manual auscultatory and automatic oscillometric techniques were counted.

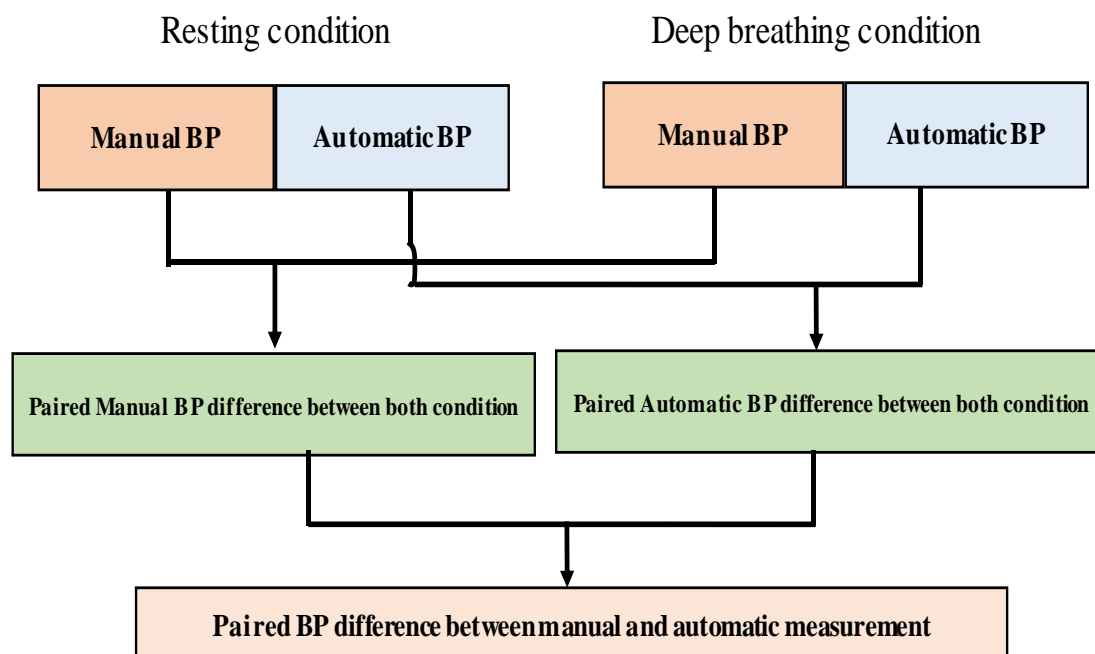


Figure 3.4: Schematic diagram of data analysis procedure for study 1.

## 3.2 Study 2: Effect of deep breathing on automatic BP of pregnant women

### 3.2.1 Subjects

Twenty healthy pregnant women (aged 19 to 55 years old, and gestational age from three to nine months) were recruited to participate in this study. Any subjects with known history of cardiovascular diseases or other pregnancy-related diseases were excluded from the study. A total of twenty subjects were excluded because of the exclusion criteria. An ethical permission was received from the Park Lane Hospital, Enugu State, Nigeria.

### 3.2.2 Preparation before BP measurement on pregnant subjects

The same preparation as discussed in section 3.1.2 is also applied here.

### 3.2.3 Measurement room

All the measurements in this study was undertaken by one experienced observer at the antenatal clinic in the Park Lane hospital. The room was kept tidy to make subjects feel comfortable during the measurement. The subjects were required to keep still as not to get distracted during the measurements.

### 3.2.4 Measurement protocol and procedure

Figure 3.5 shows the block diagram of the measurement system of study 2. As shown, a clinically validated automatic BP device (Motech Truescan model BPU 500) was used to obtain automated BPs from pregnant women at different timings: before, during and after deep breathing.

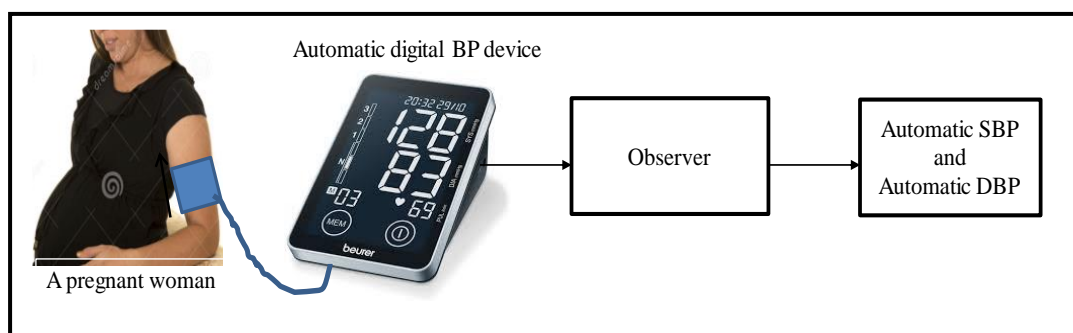


Figure 3.5: Block diagram of BP measurement system for study 2.



Before each measurement, all residual air in the cuff was pushed out before wrapping it round the arm. The automated BP device was then placed properly on the table.

Figure 3.6 shows the BP measurement protocol of study 2. For each subject, 5 minutes rest was given before first baseline BP measurement. The subject was then asked to start deep breathing at their own comfortable rate. After the fifth cycle of inhalation and exhalation, while the subject continued breathing, the second BP measurement was obtained. After this, 1 minute rest was given before the third measurement. A repeat session was performed for the whole procedure, giving a total of 6 measurements for each subject. A total of 120 BP measurements were obtained for all the 20 subjects.

All the BP data collected from each subject were recorded on the designed data collection form. Other information included are: date and time of measurement, name, address, age, gestational age, arm circumference and other pregnancy information.

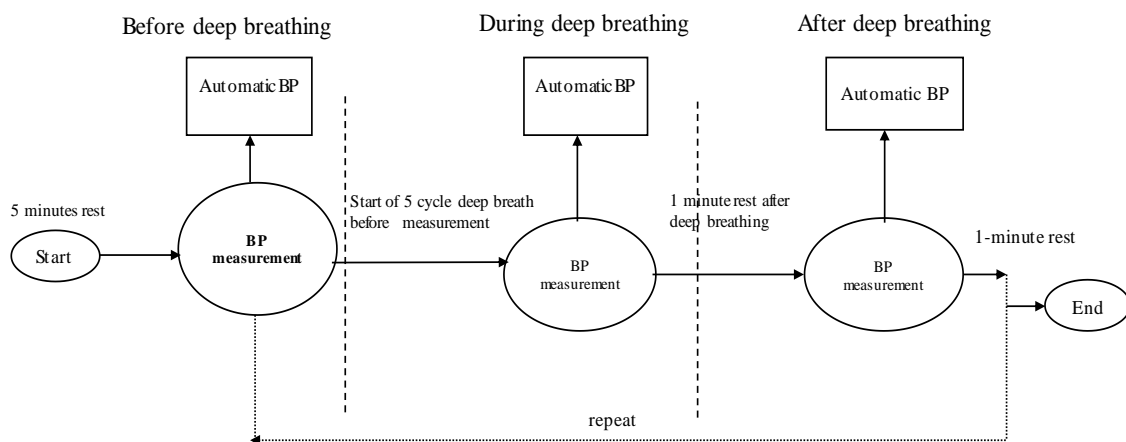


Figure 3.6: Measurement protocol of study 2.

### 3.2.5 Data and statistical analysis

The data analysis for study 2 was performed using Excel and SPSS. All the automated BP values in data collection forms were transferred into excel, where the means and standard deviation (SD) of automated BPs were calculated across all the subjects separately for the three conditions (before, during and after deep breathing). Next, Bland-Altman plots were produced to demonstrate measurement repeatability. SPSS

Statistics 17 software package (SPSS Inc., USA) was used to investigate measurement repeatability and the effect of deep breathing on automated BPs of pregnant women using ANOVA. Post-hoc multiple comparison was then used to study within-subject BP decrease during and after deep breathing in comparison with resting condition (before deep breathing). The BP changes ‘during and after deep breathing’ in comparison with ‘before deep breathing’ were presented in mean difference  $\pm$  SEM of difference. A p-value below 0.05 was considered statistically significant. Figure 3.7 displays the block diagram of automated BP comparison for the three conditions.

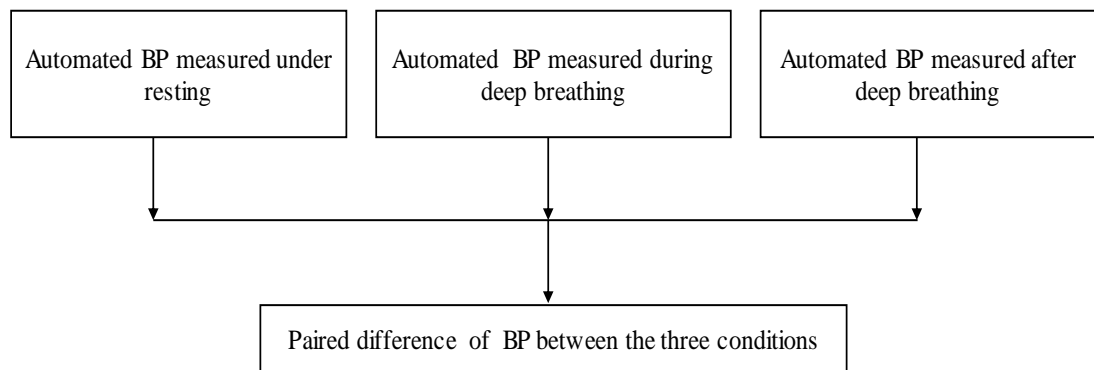


Figure 3.7: Block diagram of automated BP comparison for study 2.

## CHAPTER 4 Results

This chapter presents descriptive and analytical results from both studies: the simultaneous effect of deep breathing on manual and automated BP and the effect of deep breathing on automated BP on pregnant women.

### 4.1 Results from study1:

#### (Simultaneous effect of deep breathing on manual and automated BPs)

##### 4.1.1 Subject information

Table 4.1 summarizes the detailed subject demographic information, including age, arm circumference, height and weight.

Table 4.1: Demographic data of the subjects in study 1

No of Subjects	39		
No of Male	24		
No of Female	15		
Age (Years)	18	75	47
Height (cm)	152	192	172
Weight (kg)	50	105	78
Arm circumference (cm)	24	33	29

##### 4.1.2 Measurement repeatability on manual and automated BP measurements

The repeatability test showed that manual SBP, MAP and DBP were not statistically significant with p-values of 0.48, 0.64 and 0.27 respectively, and also for automated SBP, MAP and DBP with p-values 0.82, 0.51 and 0.34 respectively. The average BP values from the two repeats were then used as reference values for each subject.

##### 4.1.3 Effect of deep breathing on manual and automated BP

Table 4.2 and figure 4.1 give the overall mean and standard deviation (mean  $\pm$  SD) of BP under resting and deep breathing conditions for both manual auscultatory and automatic oscillometric techniques. BP changes with deep breathing for both manual

and automated BPs in comparison with resting condition are clearly shown. There was no gender difference in BP between male and female subjects ( $P>0.05$ ).

Table 4.2: Overall mean and SD of BPs under resting and deep breathing conditions. The the mean BP difference in comparison with resting condition and standard error mean (SEM) of their differences are also given.

BP parameter	Manual BPs (mmHg)			Automatic BPs (mmHg)		
	Resting (Mean $\pm$ SD)	Deep breathing (Mean $\pm$ SD)	(Mean difference $\pm$ SEM)	Resting (Mean $\pm$ SD)	Deep breathing (Mean $\pm$ SD)	(Mean difference $\pm$ SEM)
SBP	114.1 $\pm$ 10.3	110.5 $\pm$ 8.6	3.5 $\pm$ 0.9	122.3 $\pm$ 8.9	120.3 $\pm$ 8.2	2.0 $\pm$ 0.8
MAP	89.0 $\pm$ 7.4	85.3 $\pm$ 6.4	3.7 $\pm$ 0.6	89.0 $\pm$ 8.3	85.5 $\pm$ 7.1	3.4 $\pm$ 0.8
DBP	76.4 $\pm$ 7.2	72.6 $\pm$ 6.1	3.7 $\pm$ 0.6	65.6 $\pm$ 7.2	62.4 $\pm$ 6.0	3.2 $\pm$ 0.6

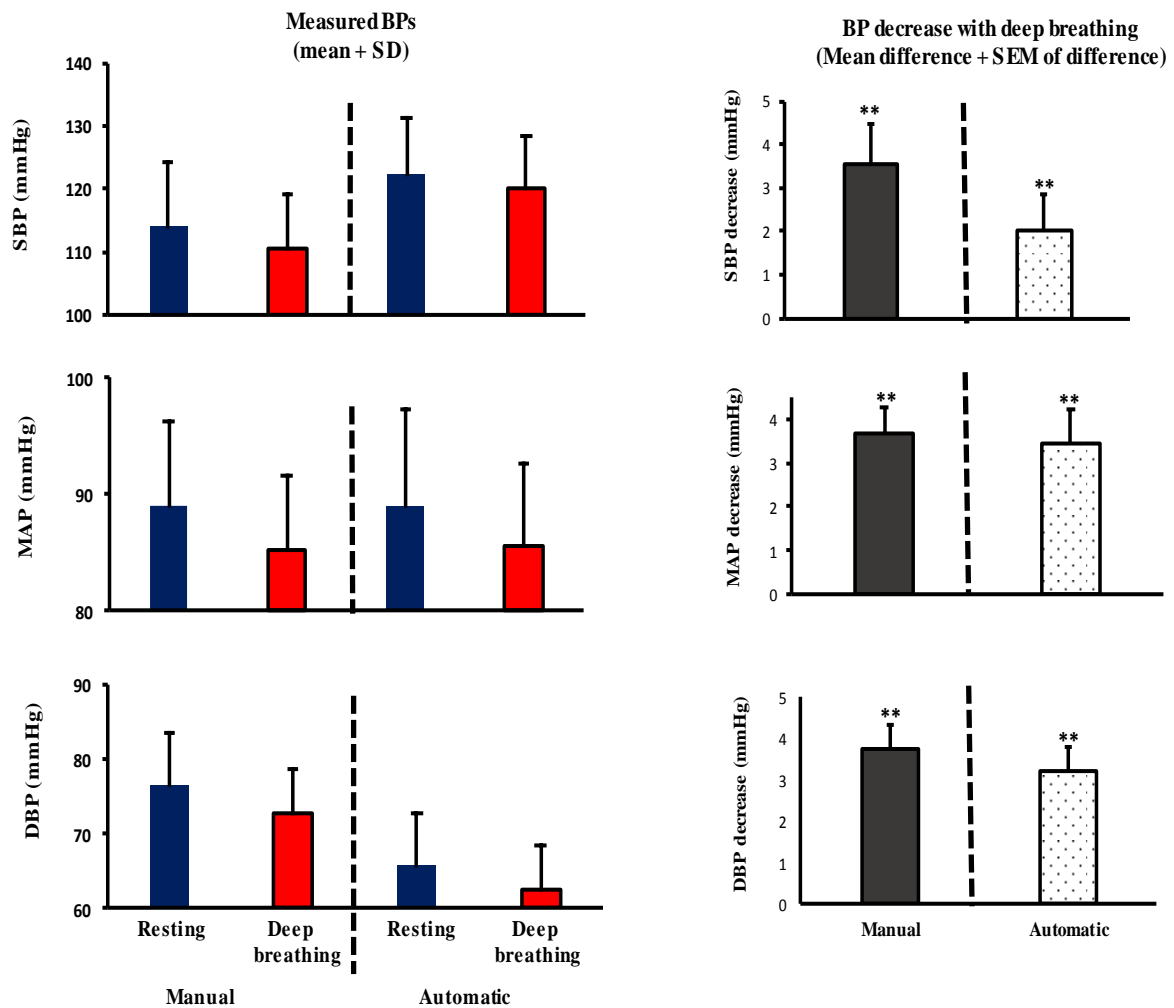


Figure 4.1: Left: Manual and automated systolic blood pressures (SBPs), mean arterial pressures (MAPs) and diastolic blood pressures (DBPs) measured under both resting and deep breathing conditions. Error bars are from between subject standard deviation (SD). Right: BP decreases with deep breathing using mean BP decrease and standard error mean (SEM) of BP decrease (\*\* indicates  $p < 0.001$  in comparison with resting condition, from one way ANOVA with repeated measures).

To be specific, manual SBP, MAP and DBP decreased significantly (all  $p<0.001$ ) with deep breathing by  $3.5 \pm 5.9$  mmHg ( $110.5 \pm 8.6$  vs  $114.1 \pm 10.3$  mmHg),  $3.7 \pm 3.7$  mmHg ( $85.3 \pm 6.4$  vs  $89.0 \pm 7.4$  mmHg) and  $3.7 \pm 3.7$  mmHg ( $72.6 \pm 6.1$  vs  $76.4 \pm 7.2$  mmHg) respectively. Similarly, automated SBP, MAP and DBP also decreased significantly (all  $p<0.001$ ) by  $2.0 \pm 5.2$  mmHg ( $120.3 \pm 8.2$  vs  $122.3 \pm 8.9$  mmHg),  $3.4 \pm 4.7$  mmHg ( $85.5 \pm 7.1$  vs  $89.0 \pm 8.3$  mmHg) and  $3.2 \pm 3.8$  mmHg ( $62.4 \pm 6.0$  vs  $65.6 \pm 7.2$  mmHg), respectively.

Figure 4.2 gives their Bland-Altman plots to illustrate the level of BP reduction with deep breathing measured simultaneously by manual and automatic techniques. To visualize the underlying principle of how automated BP decreased with deep breathing in comparison to that under resting condition. Figure 4.3 gives an example of oscillometric waveform under both resting and deep breathing conditions, and shows a clear shift of SBP, MAP and DBP toward lower pressure region when the waveforms was recorded with deep breathing.

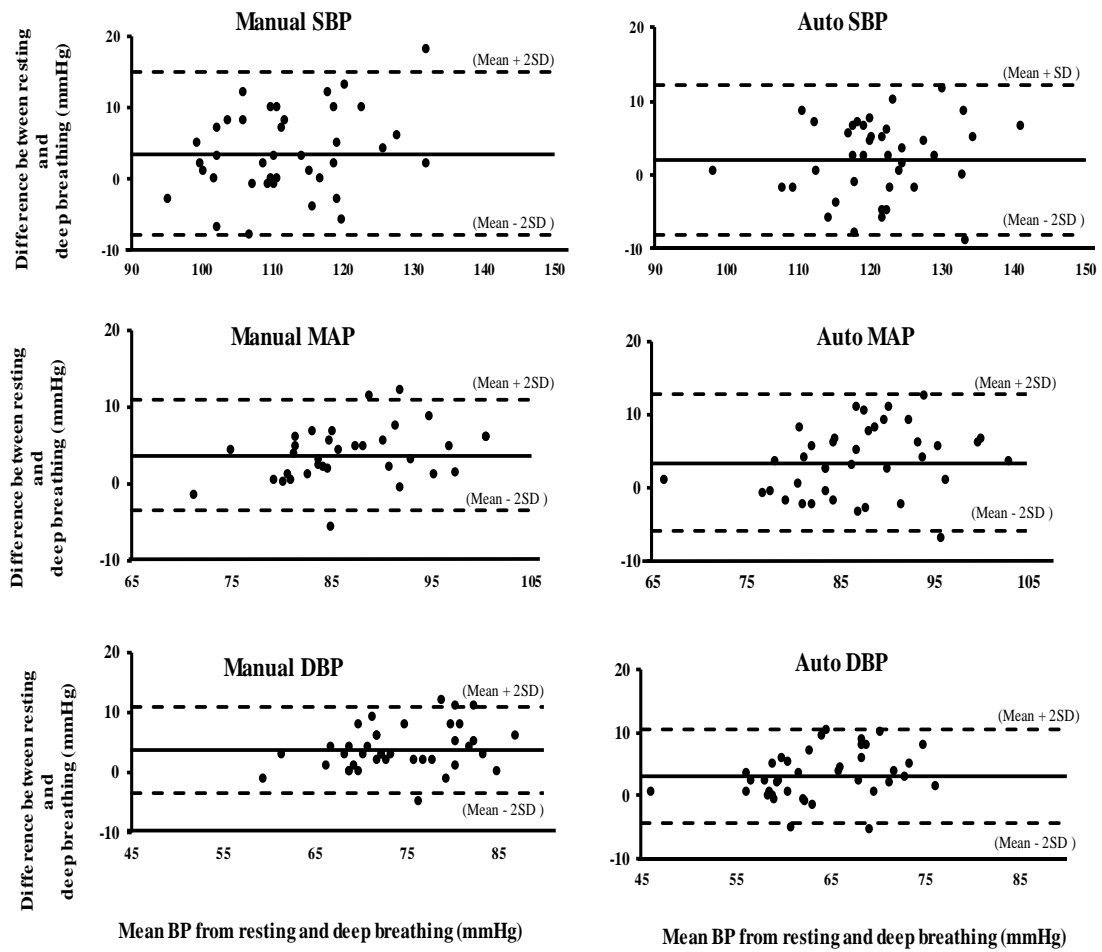


Figure 4.2: Bland-Altman plots showing BP changes with deep breathing, separately for manual and automatic techniques. The limits of agreement (mean $\pm$ 2SD) are shown.

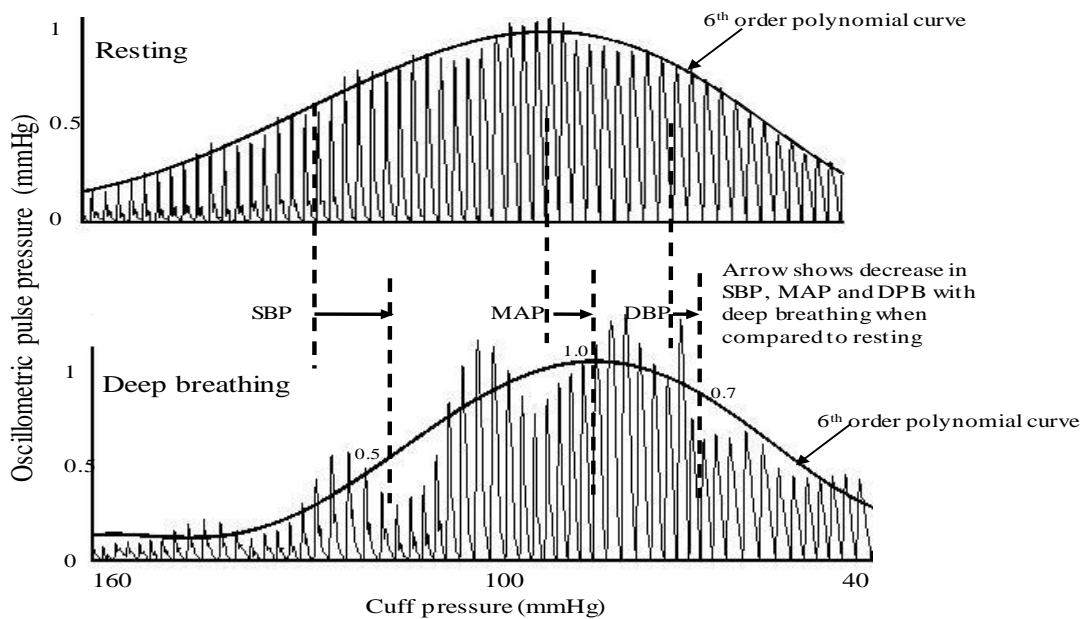


Figure 4.3: Example of oscillometric waveforms illustrating decreased automated systolic blood pressure (SBP), mean arterial pressure (MAP) and diastolic blood pressure (DBP) with deep breathing in comparison with resting condition.

#### 4.1.4 Comparison of manual and automated BP decreases with deep breathing

Figure 4.4 shows the manual BP decrease against automatic BP decrease with deep breathing. Figure 4.5 shows their Bland-Altman plots. The results, as shown in the shaded area of Figure 4.4, show that 56%, 62% and 67% of subjects had SBP, MAP and DBP reduction from both manual and automatic techniques.

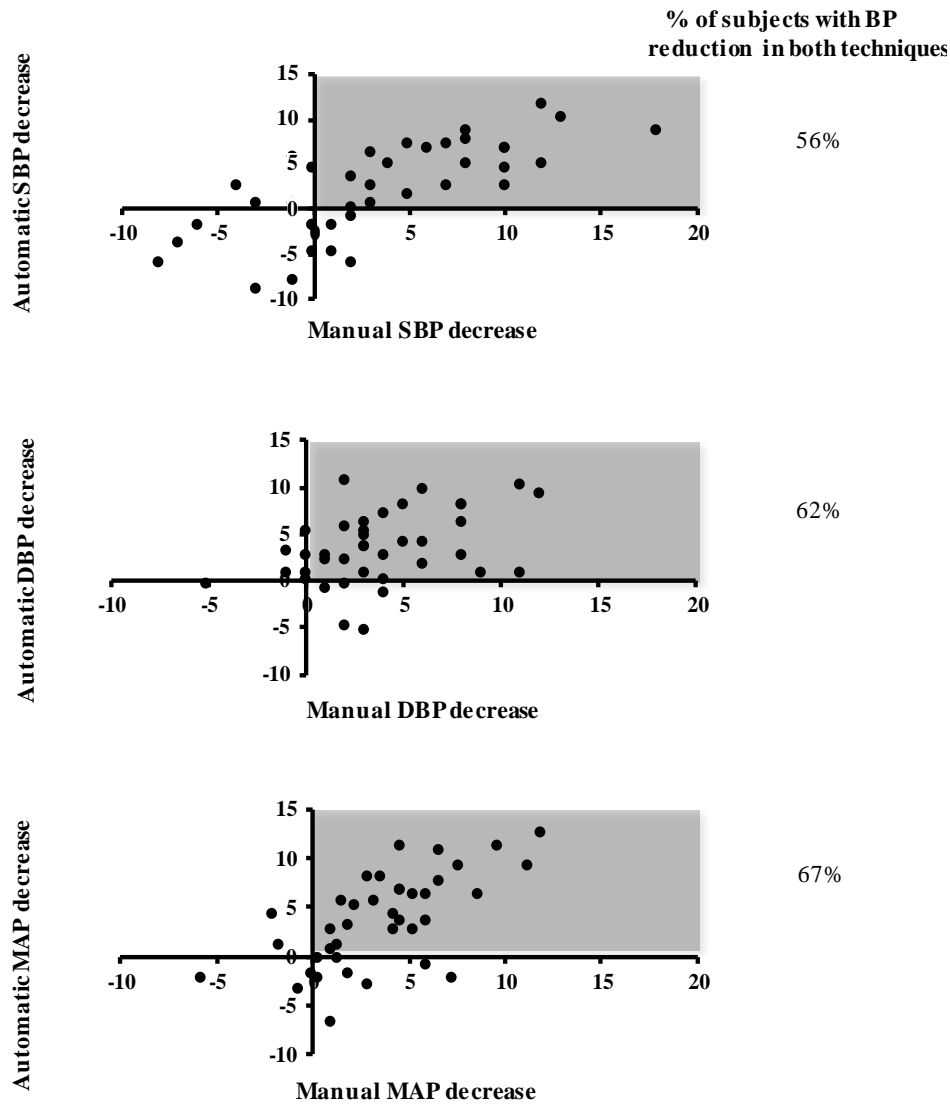


Figure 4.4: Comparison of manual and automatic BP decreases with deep breathing. 56%, 62% and 67% of subjects had SBP, MAP and DBP reduction in both manual auscultatory and automatic oscillometric techniques.

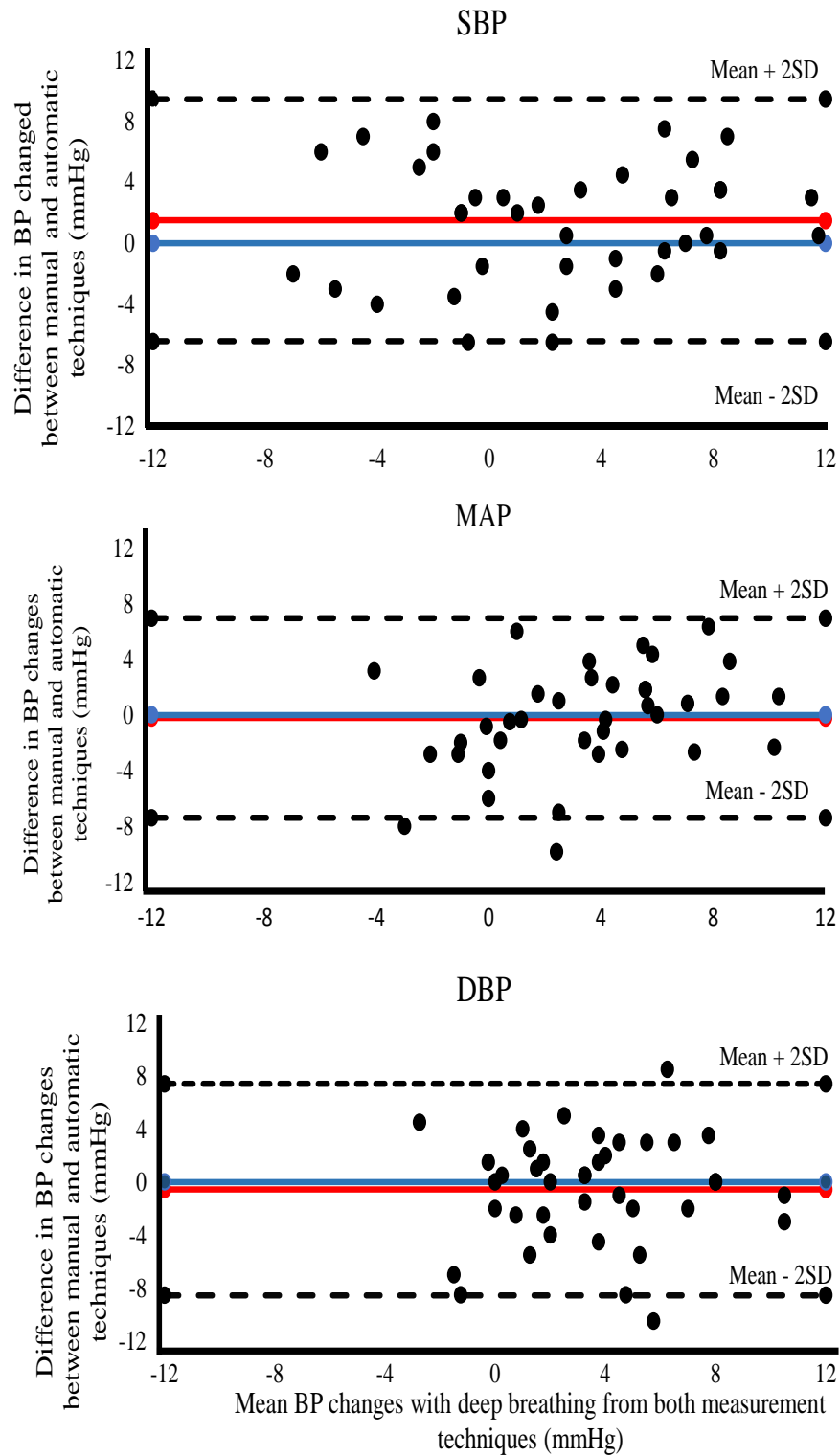


Figure 4.5: Bland Altman plots of BP changes with deep breathing between manual auscultatory and automatic oscillometric techniques.



## 4.2 Results from study 2: (Effect of deep breathing on automated BP of pregnant women)

### 4.2.1 Subject information

Table 4.3 summarizes the detailed subject demographic information including number of times of pregnancy, gestational age, arm circumference and age.

Table 4.3: Demographic data of pregnant women in study 2.

Subjects Information	Minimum	Maximum	Mean	Standard Deviation
Group of Subjects	Pregnant women			
No of subjects	20			
First pregnancy	10			
Pregnancy $\geq$ second time	10			
Gestational Age (weeks)	9	40	25	10
Age (Years)	19	37	28	5
Arm circumference (cm)	25	35	29	3

### 4.2.2 Measurement repeatability of automated BP

Table 4.4 represents the mean and SD of the difference between the first and second repeat of BP measurement. For SBP, their differences were ( $-1.0 \pm 12.8$ ,  $-1.4 \pm 9.5$  and  $-1.3 \pm 7.4$ ) mmHg, respectively for the three different measurement points. The corresponding DBP differences were ( $-1.2 \pm 10.9$ ,  $0.8 \pm 6.7$  and  $-1.1 \pm 5.4$ ) mmHg, respectively. There was no significant difference between the repeats (all  $p > 0.05$ ). MAP was not considered in study 2 data analysis because the device only provided SBP and DBP values. Figure 4.6 shows the level of agreement between first and second repeat by Bland-Altman plots.

Table 4.4: Mean and standard deviation (SD) of blood pressure (BP) measurement repeatability.

Mean and standard deviation (Mean $\pm$ SD) of automatic BP differences between repeatability (mmHg)			
(1st measurement – repeat)	Before deep breathing	During deep breathing	After deep breathing
SBP	$-1.0 \pm 12.8$	$-1.4 \pm 9.5$	$-1.3 \pm 7.4$
DBP	$-1.2 \pm 10.9$	$0.8 \pm 6.7$	$-1.1 \pm 5.4$

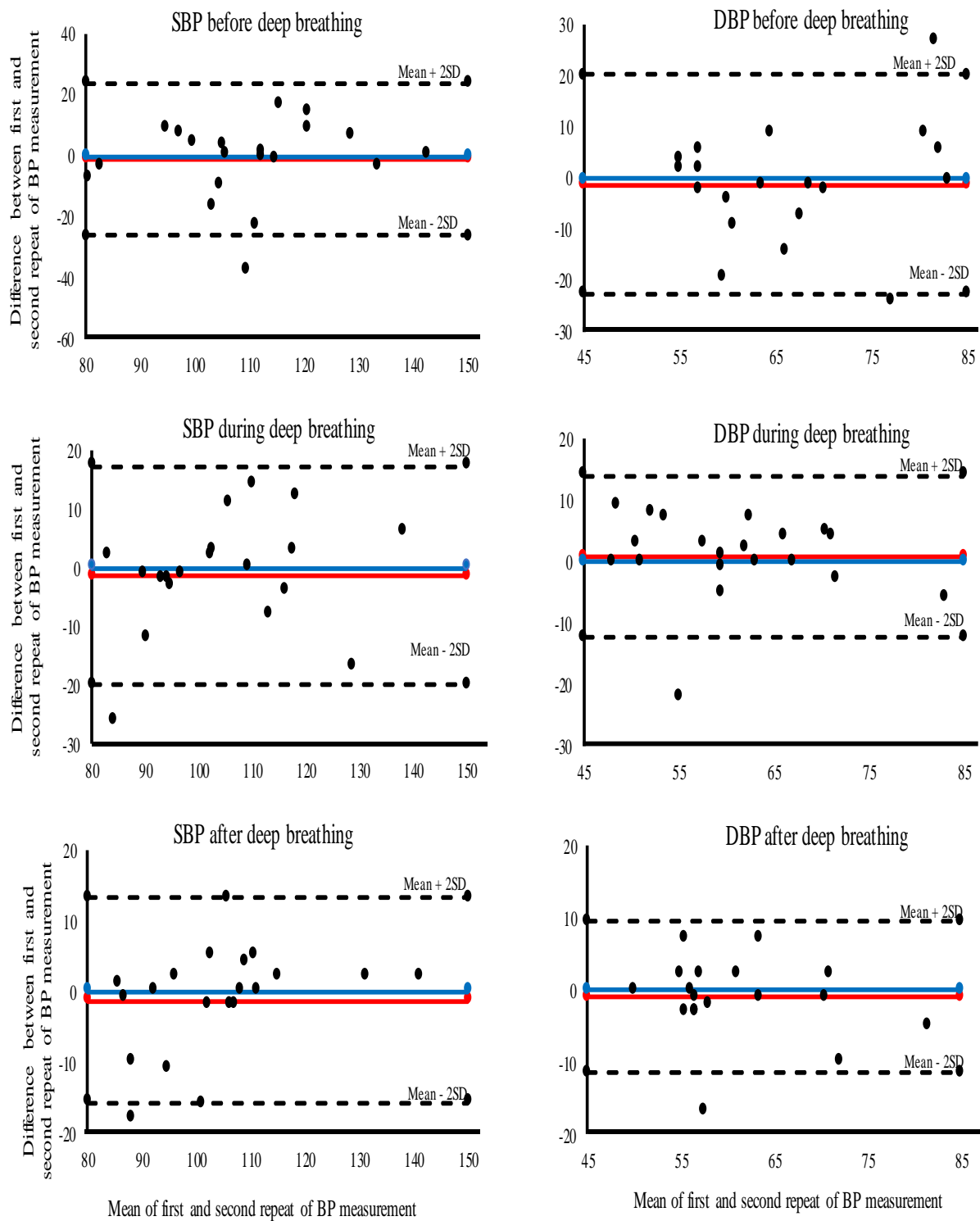


Figure 4.6: Bland-Altman plots showing the measurement repeatability between the first and second repeat measurements. The limits of agreement (mean difference  $\pm$  2SD) are given.

### 4.2.3 Comparison of automatic BP measured before, during and after deep breathing

Table 4.5 shows the mean  $\pm$  SD of automated SBP and DBP across all subjects with the measurement taken before, during and after deep breathing. It shows that SBP decreased significantly by  $6.4 \pm 11.3$  mmHg ( $103.2 \pm 15.7$  vs  $109.6 \pm 15.4$  mmHg) during deep breathing and by  $5.6 \pm 9.6$  mmHg ( $104.0 \pm 14.2$  vs  $109.6 \pm 15.4$  mmHg) after deep breathing when compared with before deep breathing respectively. Similarly, DBP reduced significantly by  $4.9 \pm 6.8$  mmHg ( $60.6 \pm 9.1$  vs  $65.4 \pm 10.9$  mmHg) during deep breathing and  $4.5 \pm 8.4$  mmHg ( $60.9 \pm 9.8$  vs  $65.4 \pm 10.9$  mmHg) after deep breathing respectively, when compared with before deep breathing.

Figure 4.7 shows the comparison of automated SBP and DBP measured before, during and after deep breathing. Both SBP and DBP decreased significantly during deep breathing with  $p=0.001$  when compared with before deep breathing. Automated SBP and DBP decreased significantly after deep breathing with  $p$  values of 0.003 and 0.001 respectively. There was no significant difference ( $p > 0.05$ ) for both SBP and DBP between during and after deep breathing.

Table 4.5: Mean and standard deviation (SD) of automated SBP and DBP measured before, during and after deep breathing. Their decreases during and after deep breathing are presented in mean changes and standard error mean (SEM) of changes.

(Mean $\pm$ SD) of automatic BPs from pregnant women (mmHg)				BP decrease with deep breathing ( Mean difference + SEM )	
BP parameter	Before deep breathing	During deep breathing	After deep breathing	During	After
<b>SBP</b>	$109.6 \pm 15.4$	$103.2 \pm 15.7$	$104.0 \pm 14.2$	$6.4 \pm 2.5$	$5.6 \pm 2.1$
<b>DBP</b>	$65.4 \pm 10.9$	$60.6 \pm 9.1$	$60.9 \pm 9.8$	$4.9 \pm 1.5$	$4.5 \pm 1.9$

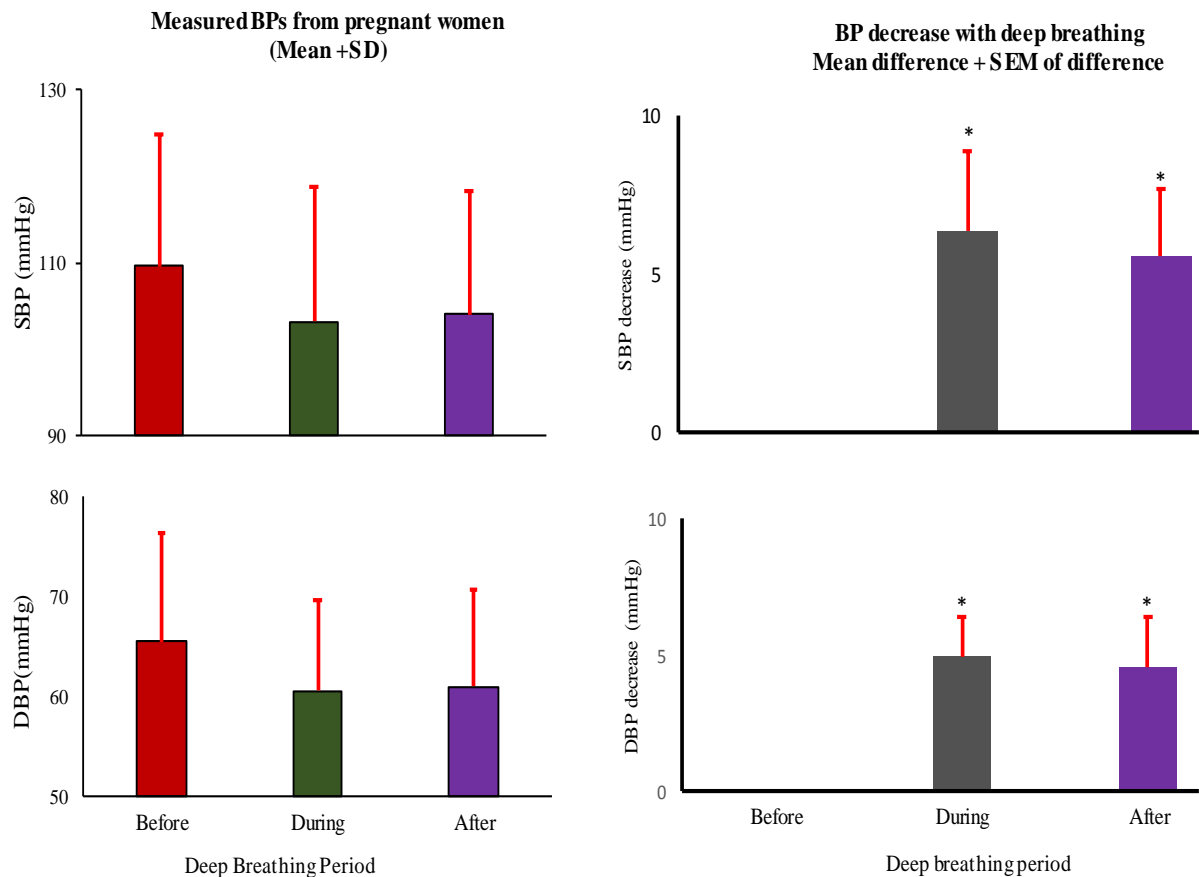


Figure 4.7: Left: automated SBP and DBP measured before, during and after deep breathing (mean + SD); Right: BP decreases during and after deep breathing (mean difference + SEM of difference) (\* indicates  $p < 0.05$  in comparison with the values before deep breathing).

#### 4.2.4 Individual BP changes before, during and after deep breathing

Figure 4.8 shows the individual SBP changes before, during and after deep breathing. Each line represents each subject and BP changes. It is observed that 75% of the subjects had SBP reduction during deep breathing and 70% of subjects after deep breathing. Similarly, Figure 4.9 shows the individual DBP changes before, during and after deep breathing. It is observed that 75% of the subjects had DBP reduction during deep breathing and the same percentage of subjects had DBP reduction after deep breathing.

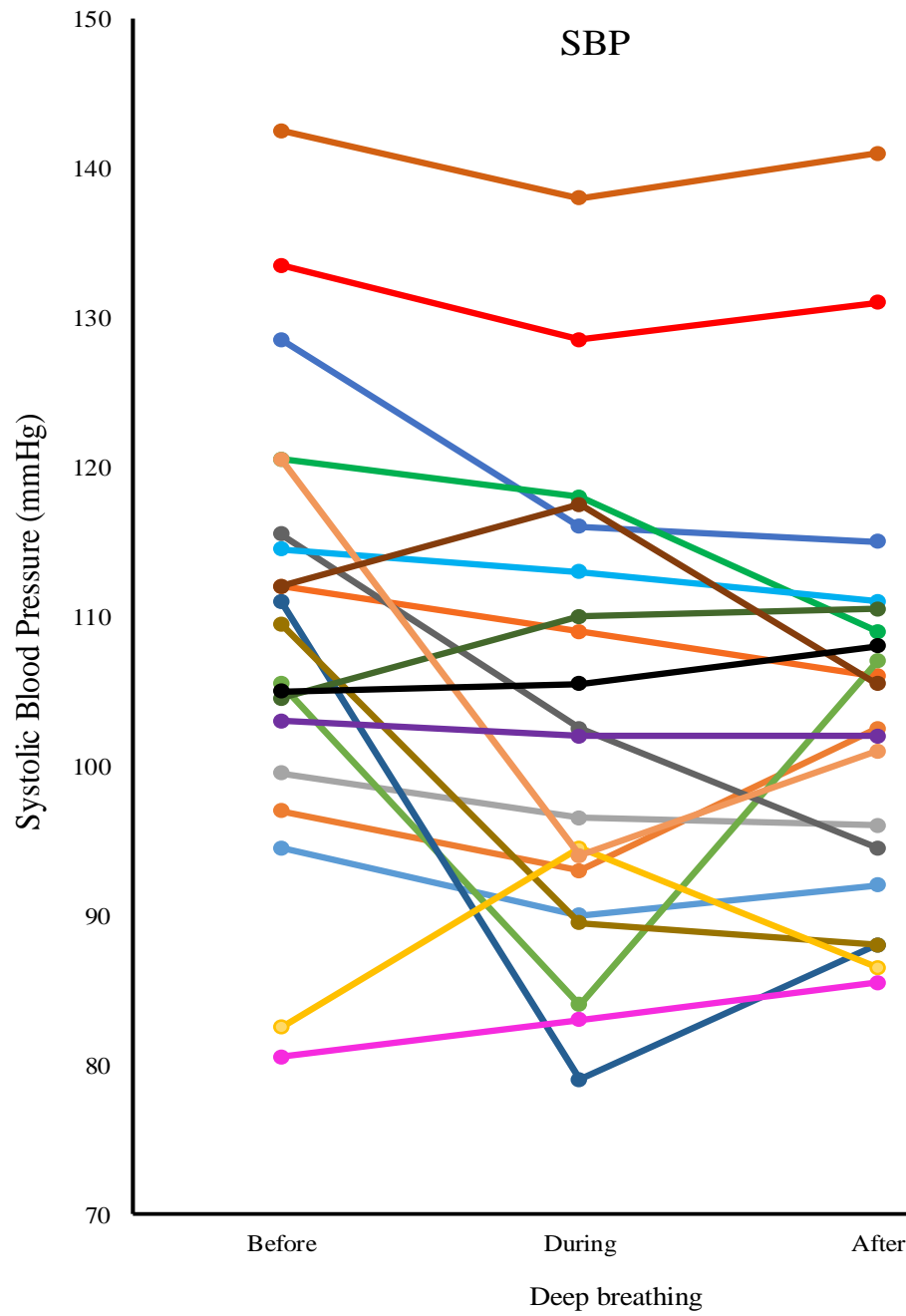


Figure 4.8: Individual automated systolic blood pressure (SBP) values measured before, during and after deep breathing in pregnant women.

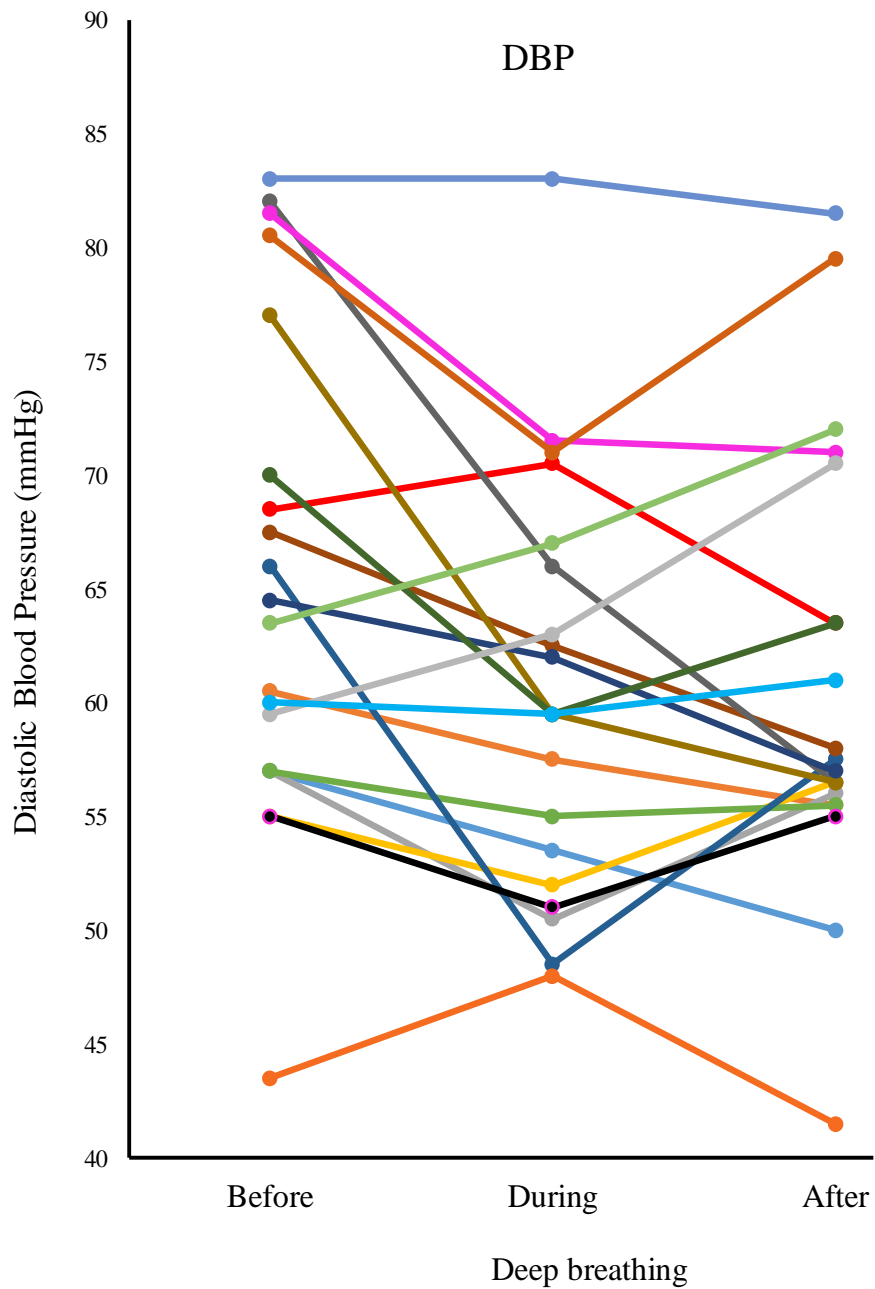


Figure 4.9: Individual automated diastolic blood pressure (DBP) measured before, during and after deep breathing in pregnant women.

## **CHAPTER 5 Discussion, conclusion and future work**

The chapter gives the conclusion, and discusses some challenges faced during the study and recommendations for future work.

### **5.1 Discussion**

This research work included two sub-studies. The first study quantitatively confirmed that both manual and automated BP decreased significantly with deep breathing when compared with resting condition. The second study, as a pilot study, demonstrated that deep breathing could be potentially used to reduce BP for some pregnant women.

#### **5.1.1 Discussion on study 1: (Simultaneous effect of deep breathing on manual and automated BPs)**

This study quantitatively demonstrated that both manual and automated BPs decreased significantly with deep breathing when compared to resting condition. In terms of the changes on manual BP, this is in agreement with previous studies that manual SBP and DBP reduced with consistent practical period of slow and regular deep breathing (Rosenthal, et al., 2000; Schein, et al., 2001; Rosenthal, et al., 2001; Jagomagi, et al., 2003; Augustovski, et al., 2004; Zheng, Giovannini and Murray, 2012). Similarly, the automated SBP and DBP decrease with deep breathing also agreed with published studies with measurements taken from different automatic BP devices (Ravi, Narasimhaswamy and Anand, 2000; Grossman, et al., 2001; Viskoper, et al., 2003; Elliott, et al., 2004; Elliott and Izzo, 2006; Parati and Carretta, 2007).

Unfortunately, there is no quantitative scientific data available on simultaneous comparison of the effect of deep breathing on both manual and automated BPs. Our research work achieved this.

Furthermore, current automatic BP devices are not validated for non-resting conditions, making results from past studies (See table 2.6a) questionable. Our research work was conducted based on the analysis of digitally recorded oscillometric cuff pressure

waveform to determine automated BPs, alleviating the potential uncertainty of the results from these un-validated automatic BP devices for non-resting conditions.

In this research, a decrease in manual auscultatory BPs with deep breathing has been confirmed with a shift of peak of automatic oscillometric waveform envelope to lower BP region (Figure 4.3). BP decreases observed in manual auscultatory technique were moderately correlated with decreases of automated BPs determined from automatic oscillometric technique, indicating true physiological effect during deep breathing.

Regarding the underlying mechanisms for the effect of deep breathing on BP, it could include:

- 1) It has been attributed to reflexes from mechanoreceptors in the lungs. When the lungs expand during deep breathing, these receptors initiate the Hering-Breuer Reflex (HBR), and reduces respiratory rate which eventually leads to autonomic cardiovascular inhibition and reduces BP (Eckberg and Sleight, 1992; Jerath, et al., 2006; Hubbard, and Falco, 2015; Adhana, et al., 2016; Onen, et al., 2016).
- 2) Deep and slow breathing decreases peripheral resistance and increases blood flow in blood capillaries, which regulates heart rate, and reduces BP (Soyik, 2000; Hubbard, and Falco, 2015; Sharma and Gupta, 2016.).
- 3) Deep breathing triggers the body to absorb its full oxygen quota, exhaling out carbon-dioxide which lowers heartbeat and stabilizes BP (Selvamurthy, et al., 1983; Suckling, et al., 2016; Hubbard, and Falco, 2015).
- 4) Nitric oxide is utilized by the endothelium cells (cells that line the blood vessels) to communicate to muscles around them to slow down and relax during vasodilation. During deep breathing, the steadiness of nitric oxide is stimulated, allowing the natural relaxation of the blood vessels, thus lowering BP (Guyton, 1961; Baylis, Mitruka, and



Deng, 1992; Zatz and Baylis, 2000; ENOS Trial Investigators, 2015; Hubbard, and Falco, 2015.).

### **5.1.2 Discussion on study 2 (Effect of deep breathing on automated BP of pregnant women)**

Although the past studies have suggested that pharmacological management of PIH has no known effect on the foetus, it have been reported that women with PIH always stand the risk of cardiovascular complication either in the short or long run of their lives (Schachter, 2002; Podymow and August, 2008; Khali, et al., 2009; Magee, et al., 2014). There is need to explore an alternative management strategy. Past studies have shown that BPs from hypertensive patients could be reduced with deep breathing for a short period of time (Schein, et al., 2001; Rosenthal, et al., 2001; Grossmann, et al., 2001; Viskoper, et al., 2003; Meles, et al., 2004; Elliot, et al., 2004, Augustovski, et al., 2004; Mori, et al., 2005; Elliot and Izzo, 2006; Parati and Carretta, 2007; Mourya, et al., 2009; Surbramanian, et al., 2011; Mahti, et al., 2016; Drodz, et al., 2016; Wolff et al., 2016). However, there is no study investigating the practice of respiratory exercise for controlling of PIH. Results from this study showed that deep breathing had a positive reduction effect on SBP and DBP on normotensive pregnant women, providing the scientific evidence that deep breathing can be served as a potential substitute to pharmacological management of PIH.

## **5.2 Limitations and challenges**

There are several limitations in this research work, which should be addressed:

- 1) The relatively small number of subjects were involved. This is because the project was conducted and investigated within a short-term period;
- 2) Some subjects did not follow deep breathing procedure exactly as required. The use of guided device should be a better solution.
- 3) The effect of slow paced breathing on the foetus has not considered, and

- 4) Finally, the effect of different gestational age on BP changes with deep breathing has not been investigated.

### **5.3 Recommendations for future study**

In order for the technique of deep breathing to be adopted in clinical and community settings to reduce BP, some recommendations of future work could include:

- 1) Inclusion of large group of normal pregnant women, as well as PIH patients;
- 2) Compare the effect of different breathing patterns on BP reduction and select a breathing pattern that can quickly and reliably reduce BP;
- 3) Investigate the long-term effect of deep breathing on BP;
- 4) Investigate the difference of BP reduction with deep breathing between male and female subjects.
- 5) Investigate which BP (SBP, MAP or DBP) is most vital to be reduced for PIH patients.
- 6) Investigate the effect of gestational age on BP reduction with deep breathing;
- 7) Investigate the potential effect of slow paced breathing on the fetus;
- 8) Develop a deep breathing guided device and test its effectiveness;
- 9) Compare non-pharmacological management with drug treatment;
- 10) Consider the possibility of deriving respiratory rates from BP measurement.

### **5.4 Conclusions**

In summary, the following could be concluded from the research work:

- 1) Both manual and automatic BP decreases with deep breathing were statistically significant. Over half of the subjects achieved significant BP reduction with deep breathing in both manual and automatic techniques.
- 2) Deep breathing can be used to help some pregnant women (over 70% in this study) to reduce BP.

## References

- ACOG Committee on Obstetric Practice, 2002. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, [e-journal] 77 (1), pp.67-75.
- Adhana, R., Agarwal, M., Gupta, R. and Dvivedi, J., 2016. Effect of slow breathing training on heart rate, spontaneous respiratory rate and pattern of breathing. *International Journal of Research in Medical Sciences*, [e-journal] 4 (4), pp.1027-1030
- American College of Obstetricians and Gynecologists. (2011). *FAQs: High blood pressure during pregnancy*.
- Amro, M., Gabi, M., Khitan, M. and Zeid, J., 2015. Pregnancy Induced Microangiopathy, *Marshall Journal of Medicine*, [e-journal] 1 (1), pp.7.
- Anderson, U.D., Gram, M., Åkerström, B. and Hansson, S.R., 2015. First Trimester Prediction of Preeclampsia. *Current hypertension reports*, [e-journal] 17 (9), pp.1-8.
- Anorlu, R.I., Iwuala, N.C. and Odum, C.U., 2005. Risk factors for pre-eclampsia in Lagos, Nigeria. *Australian and New Zealand journal of obstetrics and gynaecology*, [e-journal] 45 (4), pp.278-282. Available through:
- Arulkumaran, N. and Lightstone L., 2013. Severe pre-eclampsia and hypertensive crises. *Best practical research clinical obstetrician gynaecology* 27(6), pp.877-884.
- Augustovski, F.A., Calvo, C.B., Deprati, M. and Waisman, G., 2004. The deep-breath test as a diagnostic manoeuvre for white-coat effect in hypertensive patients. *The Journal of the American Board of Family Practice / American Board of Family Practice*, [e-journal] 17 (3), pp.184-189.
- Ayyuba, R., Abubakar, I.S. and Yakasai, I.A., 2015. Umbilical artery Doppler velocimetry study on prediction of adverse pregnancy outcomes among pregnant women with hypertensive disorders in Kano, Nigeria. *Nigerian Journal of Basic and Clinical Sciences*, [e-journal] 12 (2), pp.95.
- Baylis, C., Mitruka, B. and Deng, A., 1992. Chronic blockade of nitric oxide synthesis in the rat produces systemic hypertension and glomerular damage. *The Journal of clinical investigation*, [e-journal] 90 (1), pp.278-281.
- Benmira, A., Perez-Martin, A., Schuster, I., Aichoun, I., Coudray, S., Bereksi-Reguig, F. and Dauzat, M., 2016. From Korotkoff and Marey to automatic non-invasive oscillometric blood pressure measurement: does easiness come with reliability? *Expert review of medical devices*, [e-journal]. pp.1-11.
- Benrubi, G.I., 2012. Handbook of Obstetric and Gynaecologic Emergencies. Lippincott Williams and Wilkins.

Brown, M.A., Lindheimer, M.D., de Swiet, M., Assche, A.V. and Moutquin, J., 2001. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in pregnancy*, [e-journal] 20 (1), pp.10-15.

Calder, A.A., Dunlop, W. and Dunlop, W., 1992. *High-risk pregnancy*. [e-book] Butterworth-Heinemann.

Carty, D.M., Delles, C. and Dominiczak, A.F., 2008. Novel biomarkers for predicting preeclampsia. *Trends in cardiovascular medicine*, [e-journal] 18 (5), pp.186-194.

Cernes, R. and Zimlichman, R., 2015. RESPeRATE: the role of paced breathing in hypertension treatment. *Journal of the American Society of Hypertension: JASH*, [e-journal] 9 (1), pp.38-47.

Chen, W., Zeng, Z.L., Bing, S., Li, L.Y., Wang, R. and Wan, Y., 2016. Validation of the Grandway MD2301 digital automatic blood pressure monitor according to the European Society of Hypertension International Protocol. *Blood pressure monitoring*, [e-journal].

Chesley, L.C., 1978. Hypertension disorders in pregnancy. [e-journal].

Craici, I., Wagner, S. and Garovic, V.D., 2008. Preeclampsia and future cardiovascular risk: formal risk factor or failed stress test? *Therapeutic advances in cardiovascular disease*, [e-journal] 2 (4), pp.249-259.

Davies, A. Blakeley, A.G.H. and Kidd, C. 2011. *Human Physiology* London: Churchill livingstone.

Davey, D.A. and MacGillivray, I., 1988. The classification and definition of the hypertensive disorders of pregnancy. *American Journal of Obstetrics and Gynecology*, [e-journal] 158 (4), pp.892-898.

Drife, J.O. and Magowan, B., 2004. *Clinical obstetrics and gynaecology*. [e-book] Elsevier Health Sciences.

Drozd, T., Bilo, G., Debicka-Dabrowska, D., Klocek, M., Malfatto, G., Kielbasa, G., Styczkiewicz, K., Bednarek, A., Czarnecka, D. and Parati, G., 2016. Blood pressure changes in patients with chronic heart failure undergoing slow breathing training. *Blood pressure*, [e-journal] 25 (1), pp.4-10.

Duckitt, K. and Harrington, D., 2005. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ (Clinical research ed.)*, [e-journal] 330 (7491), pp.565.

Earlybirds, 2015. Pre-eclampsia and HELLP syndrome [online].

Eckberg D. L., Sleight P. (1992). *Human Baroreflexes in Health and Disease*. Oxford: Clarendon Press

Elliott, W.J., Izzo, J.L., White, W.B., Rosing, D.R., Snyder, C.S., Alter, A., Gavish, B. and Black, H.R., 2004. Graded blood pressure reduction in hypertensive outpatients associated with use of a device to assist with slow breathing. *The Journal of Clinical Hypertension*, [e-journal] 6 (10), pp.553-559.].

Elliott, W.J. and Izzo, J.L., Jr, 2006. Device-guided breathing to lower blood pressure: case report and clinical overview. *MedGenMed : Medscape general medicine*, [e-journal] 8 (3), pp.23.

Enaruna, N., Aziken, M. and Cert, A., 2014. Safety and efficacy of Bolus administration of magnesium sulphate for preeclampsia. *Tropical Journal of Obstetrics and Gynaecology*, [e-journal] 30 (1).

ENOS Trial Investigators, 2015. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *The Lancet*, [e-journal] 385 (9968), pp.617-628

Evans, D.H., 1989. *Doppler ultrasound: Physics, instrumentation, and clinical applications*. [e-book] John Wiley & Sons.

Facchinetti, F., Allais, G., Nappi, R., D'amico, R., Marozio, L., Bertozzi, L., Ornati, A. and Benedetto, C., 2009. Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. *Cephalalgia*, [e-journal] 29 (3), pp.286-292.

Fahey, T., Murphy, D. and Hart, J.T., 2004. *High Blood Pressure*. [e-book] Class Publishing Ltd.

Farziana, S., Rina, D.S., Chan, W.J., Lee, H. K., Tay, Y.x., Sim, W. Y., 2009. Is there any relationship between body mass index and blood pressure, Dumbdumb.

Filipovský, J., Seidlerová, J., Kratochvíl, Z., Karnosová, P., Hronová, M. and Mayer Jr, O., 2016. Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients. *Blood pressure*, [e-journal] , pp.1-7.

FitzGerald, D.E. and Drumm, J.E., 1977. Non-invasive measurement of human fetal circulation using ultrasound: a new method. *British medical journal*, [e-journal] 2 (6100), pp.1450-1451.

Flaherty, B.P., Sher, M.H. and Caro, R.G., 2005. Rapid non-invasive blood pressure measuring device, [e-journal].

Fleischman, A.R., Oinuma, M. and Clark, S.L., 2010. Rethinking the definition of "term pregnancy". *Obstetrics and gynecology*, [e-journal] 116 (1), pp.136-139.

Foo, L., Tay, J., Lees, C., McEniery, C. and Wilkinson, I., 2015. Hypertension in Pregnancy: Natural History and Treatment Options. *Current hypertension reports*, [e-journal] 17 (5), pp.1-18.

Fried, R., 1993. *The psychology and physiology of breathing: In behavioral medicine, clinical psychology, and psychiatry*. [e-book] Springer Science & Business Media.

- Gilbert, J.S., Ryan, M.J., LaMarca, B.B., Sedeek, M., Murphy, S.R. and Granger, J.P., 2008. Pathophysiology of hypertension during preeclampsia: linking placental ischemia with endothelial dysfunction. *American journal of physiology.Heart and circulatory physiology*, [e-journal] 294 (2), pp.H541-50.
- Gorostidi, M., Banegas, J.R., Sierra, A., Vinyoles, E., Segura, J. and Ruilope, L.M., 2016. Ambulatory blood pressure monitoring in daily clinical practice—the Spanish ABPM Registry experience. *European journal of clinical investigation*, [e-journal] 46 (1), pp.92-98.
- Graves, J.W., Tibor, M., Murtagh, B., Klein, L., and Sheps, S.G. 2003. The Accoson Greenlight 300TM. The first non-automated mercury free blood pressure device to pass the International Protocol for blood pressure measuring devices in adults. *Blood Pressure Monitor* 3(9) pp13-17.
- Gray, P., Griffin, E., Drumm, J., Fitzgerald, D. and Duignan, N., eds. 2013. *Neonatal Physiological Measurements: Proceedings of the Second International Conference on Fetal and Neonatal Physiological Measurements* [on-line] Butterworth-Heinemann.
- Grossman, E., Grossman, A., Schein, M., Zimlichman, R. and Gavish, B., 2001. Breathing-control lowers blood pressure. *Journal of human hypertension*, [e-journal] 15 (4), pp.263-269.
- Guerrier, G., Oluyide, B., Keramarou, M. and Grais, R.F., 2013. Factors associated with severe preeclampsia and eclampsia in Jahun, Nigeria. *International journal of women's health*, [e-journal] 5, pp.509.
- Guyton, A.C., 1961. Medical Physiology. *Academic Medicine*, [e-journal] 36 (5), pp.556.
- Haines, R., Macnab, W. and Raajkumar, S., 2013. The Management of Hypertensive Disorders in Pregnancy Compliance with NICE Guidelines. [e-journal].
- Hamdani, G., Nehus, E.J., Hanevold, C.D., Sebestyen Van Sickle, J., Woroniecki, R., Wenderfer, S.E., Hooper, D.K., Blowey, D., Wilson, A., Warady, B.A. and Mitsnefes, M.M., 2016. Ambulatory Blood Pressure, Left Ventricular Hypertrophy, and Allograft Function in Children and Young Adults After Kidney Transplantation. *Transplantation*, [e-journal].
- Hartwig, V., 2015. Engineering for safety assurance in MRI: analytical, numerical and experimental dosimetry. *Magnetic resonance imaging*, [e-journal] 33 (5), pp.681-689.
- Huang, T. L., and Charyton, C., 2008. A comprehensive review of the psychological effects of brainwave entrainment. *Alternative therapy to Health Medicine*, 14(5), 38-50.
- Hubbard, K. and Falco, F.J.E., 2015. Relaxation Techniques. [e-book] 2015. Substance Abuse. Springer, pp.337-347.
- Imai, Y., Abe, K., Sasaki, S., Minami, N., Munakata, M., Sakuma, H., Hashimoto, J., Sekino, H., Imai, K. and Yoshinaga, K., 1989. Clinical evaluation of semiautomatic and automatic devices for home blood pressure measurement: comparison between cuff-oscillometric and microphone methods. *Journal of hypertension*, [e-journal] 7 (12), pp.983-990.

Imholz, B.P., Settels, J.J., van der Meiracker, A.H., Wesseling, K.H. and Wieling, W., 1990. Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. *Cardiovascular research*, [e-journal] 24 (3), pp.214-221.

Isiguzo, G.C., Baugh, D., Nwuruku, G.C., Mezue, K.N., Madu, C. and Madu, E.C., 2016. Initial experience with 24-h ambulatory blood pressure monitoring in Nigerian patients with hypertension. *Nigerian Journal of Cardiology*, [e-journal] 13 (1), pp.33.

Jagomagi, K., Raamat, R., Talts, J., Lansimies, E. and Jurvelin, J., 2003. Effect of deep breathing test on finger blood pressure. *Blood pressure monitoring*, [e-journal] 8 (5), pp.211-214.

James, D.K., Steer, P.J., Weiner, C.P. and Gonik, B., 2010. *High risk pregnancy: management options-expert consult*. [e-book] Elsevier Health Sciences.

Jerath, R., Edry, J.W., Barnes, V.A. and Jerath, V., 2006. Physiology of long pranayamic breathing: neural respiratory elements may provide a mechanism that explains how slow deep breathing shifts the autonomic nervous system. *Medical hypotheses*, [e-journal] 67 (3), pp.566-571.

Kaplan, N. M., 2001. *Treatment of Hypertension in General Practise*. London: Martin Dunitz Ltd.

Kenny, L.C., Broadhurst, D.I., Dunn, W., Brown, M., North, R.A., McCowan, L., Roberts, C., Cooper, G.J., Kell, D.B., Baker, P.N. and Screening for Pregnancy Endpoints Consortium, 2010. Robust early pregnancy prediction of later preeclampsia using metabolomic biomarkers. *Hypertension*, [e-journal] 56 (4), pp.741-749.

Khalil, A., Jauniaux, E. and Harrington, K., 2009. Antihypertensive therapy and central hemodynamics in women with hypertensive disorders in pregnancy. *Obstetrics & Gynecology*, [e-journal] 113 (3), pp.646-654.

Kim, N.C., 1994. *A study on the effect of Dan Jeon breathing method to reduce blood pressure of the client with essential hypertension*.

Kimbally, K.G., Barassoumbi, H., Buambo, S.F., Gombet, T., Kibeke, P., Monabeka, H.G., Iloki, L.H. and Ekoundzola, J.R., 2007. Arterial hypertension: epidemiological aspects and risk factors on pregnant and delivered woman. *Dakar medical*, [e-journal] 52 (2), pp.148-152.

Kintiraki, E., Papakatsika, S., Kotronis, G., Goulis, D.G. and Kotsis, V., 2015. Pregnancy-Induced hypertension. *Hormones (Athens, Greece)*, [e-journal] 14 (2), pp.211-223.

Krause, T., Lovibond, K., Caulfield, M., McCormack, T., Williams, B. and Guideline Development Group, 2011. Management of hypertension: summary of NICE guidance. *BMJ (Clinical research ed.)*, [e-journal] 343, pp.d4891.

Kuc, S., Wortelboer, E.J., van Rijn, B.B., Franx, A., Visser, G.H. and Schielen, P.C., 2011. Evaluation of 7 serum biomarkers and uterine artery Doppler ultrasound for first-trimester prediction of preeclampsia: a systematic review. *Obstetrical & gynecological survey*, [e-journal] 66 (4), pp.225-239.

- Lehrer, P.M, Vaschillo, E., Vaschillo, B., Lu, S.E., Eckberg, D.L., Edelberg, R., Shih, W.J., Lin, Y., Kuusela, T.A., Tahvanainen, K.U., and Hamer, R. M. 2003. Heart variability biofeedback increases baroreflex gain and peak expiratory flow. *Psychosomatic Medicine* 65(5), pp 796-805.
- Lemogoum, D., Seedat, Y.K., Mabadeje, A.F., Mendis, S., Bovet, P., Onwubere, B., Blackett, K.N., Lenfant, C., Kabangu, J.R. and Block, P., 2003. Recommendations for prevention, diagnosis and management of hypertension and cardiovascular risk factors in sub-Saharan Africa. *Journal of hypertension*, [e-journal] 21 (11), pp.1993-2000.
- Levine, R.J. and Lindheimer, M.D., 2009. First-trimester prediction of early preeclampsia: a possibility at last! *Hypertension*, [e-journal] 53 (5), pp.747-748.
- Llewellyn-Jones, D., 1972. The four quarters of pregnancy. *The Lancet*, [e-journal] 299 (7753), pp.737-738.
- Macgillivray, I. and Campbell, D.M., 1980. The relevance of hypertension and oedema in pregnancy. *Clinical and experimental hypertension*, [e-journal] 2 (5), pp.897-914.
- MacGregor A. G. and Kaplan M.N., 2006. *Fast Facts: Hypertension*. 3rd ed. Abingdon: Health Press Limited, Elizabeth House.
- Magee, L.A., Pels, A., Helewa, M., Rey, E. and von Dadelszen, P., 2014. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*, [e-journal] 4 (2), pp.105-145.
- Magee, L.A., Helewa, M., Moutquin, J.M., von Dadelszen, P., Hypertension Guideline Committee and Strategic Training Initiative in Research in the Reproductive Health Sciences (STIRRH) Scholars, 2008. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *Journal of obstetrics and gynaecology Canada: JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC*, [e-journal] 30 (3 Suppl), pp.S1-48.
- Magowan, B.A., Owen, P. and Thomson, A., 2014. *Clinical obstetrics and gynaecology*. [e-book] Elsevier Health Sciences.
- Mahaba, H.M., Ismail, N.A., El Damaty, S.I. and Kamel, H.A., 2001. Pre-eclampsia: epidemiology and outcome of 995 cases. *The Journal of the Egyptian Public Health Association*, [e-journal] 76 (5-6), pp.357-368.
- Mahtani, K.R., Beinortas, T., Bauza, K. and Nunan, D., 2016. Device-Guided Breathing for Hypertension: a Summary Evidence Review. *Current hypertension reports*, [e-journal] 18 (4), pp.1-5.
- Maputle, S., Khoza, L. and Lebeso, R., 2015. Knowledge towards Pregnancy-induced Hypertension among Pregnant Women in Vhembe District, Limpopo Province. [e-journal].
- Martini, F.H., and Nath, J L., 2009. *Fundamentals of Anatomy and Physiology* Pearson Education, Inc.



Martini, F.H., and Bartholomew, E.F, 2007. *Fundamentals of Anatomy and Physiology* Pearson Education, Inc.

Mason, H., Vandoni, M., Debarbieri, G., Codrons, E., Ugargol, V. and Bernardi, L., 2013. Cardiovascular and respiratory effect of yogic slow breathing in the yoga beginner: what is the best approach? *Evidence-based complementary and alternative medicine: eCAM*, [e-journal] 2013, pp.743504.

Mediblztv n.d. *Symptoms and signs of preeclampsia - Google Search* [Online].

Mehta, N., Chen, K., Hardy, E. and Powrie, R., 2015. Respiratory disease in pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology*, [e-journal].

Meles, E., Giannattasio, C., Failla, M., Gentile, G., Capra, A. and Mancina, G., 2004. Nonpharmacologic treatment of hypertension by respiratory exercise in the home setting. *American journal of hypertension*, [e-journal] 17 (4), pp.370-374.

Moini, J., 2012. *Anatomy and Physiology for Health Professionals* Jones & Barlett Learning International.

Moore Simas, T.A., Crawford, S.L., Bathgate, S., Yan, J., Robidoux, L., Moore, M. and Maynard, S.E., 2014. Angiogenic biomarkers for prediction of early preeclampsia onset in high-risk women. *The Journal of Maternal-Fetal & Neonatal Medicine*, [e-journal] 27 (10), pp.1038-1048.

Mori, H., Yamamoto, H., Kuwashima, M., Saito, S., Ukai, H., Hirao, K., Yamauchi, M. and Umemura, S., 2005. How does deep breathing affect office blood pressure and pulse rate? *Hypertension research*, [e-journal] 28 (6), pp.499.

Mourya, M., Mahajan, A.S., Singh, N.P. and Jain, A.K., 2009. Effect of slow-and-fast breathing exercises on autonomic functions in patients with essential hypertension. *Journal of alternative and complementary medicine (New York, N.Y.)*, [e-journal] 15 (7), pp.711-717.

Mulrow, C.D., 2001. *Evidence-based Hypertension*, Spain: GraphyCems,

National Collaborating Centre for Women's and Children's Health (UK), 2010. [e-journal].

National High Blood Pressure Education Program, 2004. Classification of blood pressure. [e-journal].

National Institute for Health and Care Excellence guidelines for hypertension in pregnancy, 2008. [e-journal].

O'Brien, E., Asmar, R., Beilin, L., Imai, Y., Mancina, G., Mengden, T., Myers, M., Padfield, P., Palatini, P. and Parati, G., 2005. Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self-blood pressure measurement. *Journal of hypertension*, [e-journal] 23 (4), pp.697-701.

O'Brien, E., Asmar, R., Beilin, L., Imai, Y., Mallion, J., Mancina, G., Mengden, T., Myers, M., Padfield, P. and Palatini, P., 2003. European Society of Hypertension recommendations for

conventional, ambulatory and home blood pressure measurement. *Journal of hypertension*, [e-journal] 21 (5), pp.821-848.

O'Brien, E., Beevers, G. and Lip, G.Y., 2001. ABC of hypertension. Blood pressure measurement. Part III-automated sphygmomanometry: ambulatory blood pressure measurement. *BMJ (Clinical research ed.)*, [e-journal] 322 (7294), pp.1110-1114.

Ogbole, G., Adeleye, A., Adeyinka, A. and Ogunseyinde, O., 2012. Magnetic resonance imaging: Clinical experience with an open low-field-strength scanner in a resource challenged African state. *Journal of neurosciences in rural practice*, [e-journal] 3 (2), pp.137.

Okafor, U.V., Efetie, E.R., Igwe, W. and Okezie, O., 2009. Anaesthetic management of patients with pre-eclampsia/eclampsia and perinatal outcome. *The Journal of Maternal-Fetal & Neonatal Medicine*, [e-journal] 22 (8), pp.688-692.

Olopade, F.E. and Lawoyin, T.O. 2008. Maternity mortality in a Nigerian maternity hospital, *African journal biomedical research*, 11(3), pp267-273.

Omole-Ohonsi, A. and Ashimi, A.O 2008. Pre-eclampsia: a risk study of risk factors, *Nigerian medical practitioners* 53(6), pp99-102.

Onen, M.R., Yilmaz, I., Ramazanoglu, L., Tanriverdi, O., Aydin, M.D., Kanat, A., Yolas, C. and Sipal, S., 2016. Rational Roots of Sympathetic Overactivity by Neurogenic Pulmonary Edema Modeling arising from Sympathico-Vagal Imbalance in Subarachnoid Hemorrhage: an Experimental Study. *World neurosurgery*, [e-journal].

Osungbade, K. and Ige, O., 2014. Public health perspectives of preeclampsia in developing countries: implication for health system strengthening. *Journal of Pregnancy*, [e-journal] 2014, pp.81-95.

Osungbade, K.O. and Ige, O.K., 2011. Public health perspectives of preeclampsia in developing countries: implication for health system strengthening. *Journal of pregnancy*, [e-journal] 2011, pp.481-495.

Parati, G. and Carretta, R., 2007. Device-guided slow breathing as a non-pharmacological approach to antihypertensive treatment: efficacy, problems and perspectives. *Journal of hypertension*, [e-journal] 25 (1), pp.57-61.

Park M.K., Menard, S.W. and Yuan, C., 2001. Comparison of auscultatory and oscillometric blood pressures. *JAMA Paediatrics*, 155(1) pp50-53

Pattanshetty, R.B. and Thapa, S., 2015. Effect of Early Mobilization Programme in Addition to Diaphragmatic Breathing Exercise versus Incentive Spirometry on Diaphragmatic Excursion and PEFR in Patients with Abdominal Surgery-a RCT. *Indian Journal of Physiotherapy & Occupational Therapy*, [e-journal] 9 (2), pp.28-63 .

Peters, M. and British Medical Association, associated,with work, 2013. *The British Medical Association illustrated medical dictionary*. [e-book] 3rd edition. London.

Petrie, J.C., O'Brien, E.T., Littler, W.A. and de Swiet, M., 1986. Recommendations on blood pressure measurement. *British medical journal (Clinical research ed.)*, [e-journal] 293 (6547), pp.611-615.

Pickering, T.G., Hall, J.E., Appel, L.J., Falkner, B.E., Graves, J., Hill, M.N., Jones, D.W., Kurtz, T., Sheps, S.G., Roccella, E.J. and Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research, 2005. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension*, [e-journal] 45 (1), pp.142-161.

Pipkin, F.B. and Symonds, E., 1986. Pregnancy-induced hypertension. [e-book] 1986. *Prostaglandins and their Inhibitors in Clinical Obstetrics and Gynaecology*. Springer. , pp.337-366.

Podymow, T. and August, P., 2014. Antihypertensive drugs in pregnancy. *Clinical obstetrician gynaecology* 54(4), pp.797-805.

Poulter, N., Thom, S. and Kirby M., 2001. *Shared Care for Hypertension*, Phoenix offset, HK.

Pucci, M., Sarween N., Knox E., Lipkin G., and Martin, U., 2015. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in women of childbearing age: risks versus benefits. *Pak Journal of pharmaceutical science* 28(3), pp.1015-1021.

Raisingchildren, 2014. Raising Children Network (Australia) Limited at <<http://www.raisingchildren.net.au>.

Ravi, G., Narasimhaswamy, K. and Anand, K. 2000. Effect of Short Term “Deep breathing” on Cardiovascular Functions in Young Individuals. [e-journal] pp.5-8.

Roberge, S., Giguère, Y., Villa, P., Nicolaidis, K., Vainio, M., Forest, J., von Dadelzen, P., Vaiman, D., Tapp, S. and Bujold, E., 2012. Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. *Obstetrical & gynecological survey*, [e-journal] 67 (12), pp.760-762.

Rolleston, S.H. and Camb, M., 2007. *High Blood Pressure*. [e-journal].

Rosenthal, T., Alter, A., Peleg, E. and Gavish, B., 2000. B006: Device-guided breathing exercises reduce blood pressure--ambulatory and home measurements. *American Journal of Hypertension*, [e-journal] 13 (S2), pp.56-58.

Rosenthal, T., Alter, A., Peleg, E. and Gavish, B., 2001. Device-guided breathing exercises reduce blood pressure: ambulatory and home measurements. *American Journal of Hypertension*, [e-journal] 14 (1), pp.74.

Schein, M., Gavish, B., Herz, M., Rosner-Kahana, D., Naveh, P., Knishkowsky, B., Zlotnikov, E., Ben-Zvi, N. and Melmed, R., 2001. Treating hypertension with a device that slows and regularises breathing: a randomised, double-blind controlled study. *Journal of human hypertension*, [e-journal] 15 (4), pp.271-278.

Schenone, A.L., Giugni, G., Schenone, M.H., Diaz, L., Bermudez, A., Majdalany, D. and Sosa-Olavarria, A., 2015. Evaluation of Fetal Pulmonary Veins during Early Gestation by Pulsed Doppler Ultrasound: A Feasibility Study. *Journal of Fetal Medicine*, 2 (1), pp.27-32.

Seeley, R. R., Stephens, T. D. and Tate, P.T., 1995. *Anatomy and physiology*, 3rd ed Missouri: Mosby.

Selvamurthy, W, Nayar, H.S, Joseph, N.T, and Joseph S., 1983. Physiological effects of yogic practice. *NIMHANS Journal*. (1) pp.71-80.

Shapiro, D., Jamner, L.D., Lane, J.D., Light, K.C., Myrtek, M., Sawada, Y. and Steptoe, A., 1996. Blood pressure publication guidelines. *Psychophysiology*, [e-journal] 33 (1), pp.1-12.

Sharma, N. and Gupta, R., 2016. A study of yoga in anemic patients. *International Journal of Medical Science and Public Health*, [e-journal] 5 (3), pp.399-401.

Sharma, N., Mala, M.D., Frishman., William, H., Gandhi., and Kaushang, M. D., 2011. ResPerate: Nonpharmacological Treatment of Hypertension *Cardiology in Review* [e-journal] 19 (2), pp.47-51.

Sharman, J.E., Howes, F.S., Head, G.A., McGrath, B.P., Stowasser, M., Schlaich, M., Glasziou, P. and Nelson, M.R., 2016. How to measure home blood pressure: Recommendations for healthcare professionals and patients. *Australian Family Physician*, 45 (1), pp.31.

Shennan, A., 2016. Pre-eclampsia and non-proteinuric pregnancy induced hypertension. *Obstetrics and gynaecology: an evidence-based text for MRCOG*, [e-journal].

Sibai, B.M., 1990. *Preeclampsia-eclampsia*. [e-book] Year Book Medical Publishers.

Sibai, B.M., 2003. Diagnosis and management of gestational hypertension and preeclampsia. *Obstetrics and gynecology*, [e-journal] 102 (1), pp.181-192.

Sibai, B.M. and Stella, C.L., 2009. Diagnosis and management of atypical preeclampsia-eclampsia. *American Journal of Obstetrics and Gynecology*, 200 (5), pp.481.e1-481.e7.

Sisson, M., 2012. The primal blueprint: updated and expanded edition. Primal Nutrition. Inc, Malibu, CA.

Sovik, R. 2000. The science of breathing-the yogic view. *Progress brain research*.122, pp. 491-505

Subramanian, H., Soudarssanane, M.B., Jayalakshmy, R., Thiruselvakumar, D., Navasakthi, D., Sahai, A. and Saptharishi, L., 2011. Non-pharmacological Interventions in Hypertension: A Community-based Cross-over Randomized Controlled Trial. *Indian journal of community medicine: official publication of Indian Association of Preventive & Social Medicine*, [e-journal] 36 (3), pp.191-196.

Suckling, R.J., He, F.J., Markandu, N.D. and MacGregor, G.A., 2016. Modest Salt Reduction Lowers Blood Pressure and Albumin Excretion in Impaired Glucose Tolerance and Type 2

Diabetes Mellitus: A Randomized Double-Blind Trial. *Hypertension*, [e-journal] 67 (6), pp.1189-1195

Suzuki, Y., Matsuura A., and Yamamoto T., 2015. Management of pregnancy induced hypertension. *Nihon Rinsho*.73 (11), pp1897-1903.

Syed, M.I. and Ramanappa, M., 2014. The Role of Umbilical Artery Doppler in Predicting the Fetal Out Come in Cases of Pregnancy Induced Hypertension. *Indian Journal of Mednodent and Allied Sciences*.

Symonds, E.M., Symonds, I.M. and Arulkumaran, S., 2013. *Essential obstetrics and gynaecology*. [e-book] Elsevier Health Sciences.

Teklu, S. and Gaym, A., 2006. Prevalence and clinical correlates of the hypertensive disorders of pregnancy at Tikur Anbessa Hospital, Addis Ababa, Ethiopia. *Ethiopian medical journal*, [e-journal] 44 (1), pp.17-26.

Ter Haar, G.R., Abramowicz, J.S., Akiyama, I., Evans, D.H., Ziskin, M.C. and Maršál, K., 2013. Do we need to restrict the use of Doppler ultrasound in the first trimester of pregnancy? *Ultrasound in medicine & biology*, [e-journal] 39 (3), pp.374-380.

Thiam, M., Goumbala, M., Gning, S., Fall, P. and Cellier, C., 2003. [Maternal and fetal prognosis for hypertension in pregnancy in sub-Saharan Africa (Senegal)]. *JournalÂ de GynÂcologie ObstÂtrique et Biologie de la Reproduction*, [e-journal] 32 (1), pp.35-38.

Thibodeau, P., 2010. *Anatomy and Physiology* 7th ed. Missouri: Mosby Elsevier

Thomson, A.M., Hytten, F.E. and Billewicz, W.Z., 1967. The epidemiology of oedema during pregnancy. *The Journal of obstetrics and gynaecology of the British Commonwealth*, [e-journal] 74 (1), pp.1-10.

Tomicic, M., Petric, D., Rumboldt, M., Carevic, V. and Rumboldt, Z., 2015. Deep breathing: A simple test for white coat effect detection in primary care. *Blood pressure*, [e-journal] 24 (3), pp.158-163.

Topouchian, J., Agnoletti, D., Blacher, J., Youssef, A., Chahine, M.N., Ibanez, I., Assemani, N. and Asmar, R., 2014. Validation of four devices: Omron M6 Comfort, Omron HEM-7420, Withings BP-800, and Polygreen KP-7670 for home blood pressure measurement according to the European Society of Hypertension International Protocol. *Vascular health and risk management*, [e-journal] 10, pp.33-44.

Tortora, G. and Derrickson, B., 2007. *Principles of anatomy & physiology* 11<sup>th</sup> ed. Binder ready version.

Unit, B., 2001. Blood pressure measuring devices: recommendations of the European Society of Hypertension. *BMJ*, [e-journal] 322, pp.531-536.

Vadhera R. B., and Simon, M., 2015. Hypertensive emergencies in pregnancy. *Expert revolution in clinical pharmacology* 8(2), pp.221-231.

Venes, D., 2013. *Taber's cyclopedic medical dictionary*. [e-book] FA Davis.

Villar, J., Carroli, G., Wojdyla, D., Abalos, E., Giordano, D., Ba'aqeel, H., Farnot, U., Bergsjø, P., Bakketeig, L. and Lumbiganon, P., 2006. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *American Journal of Obstetrics and Gynecology*, [e-journal] 194 (4), pp.921-931.

Visintin, C., Mugglestone, M.A., Almerie, M.Q., Nherera, L.M., James, D., Walkinshaw, S. and Guideline Development Group, 2010. Management of hypertensive disorders during pregnancy: summary of NICE guidance. *BMJ (Clinical research ed.)*, 341, pp.220-227.

Viskoper, R., Shapira, I., Priluck, R., Mindlin, R., Chornia, L., Laszt, A., Dicker, D., Gavish, B. and Alter, A., 2003. Nonpharmacologic treatment of resistant hypertensives by device-guided slow breathing exercises. *American journal of hypertension*, 16 (6), pp.484-487.

Weber, M.A. and Turner, J.R., 2016. Ambulatory Blood Pressure Monitoring: New Directions and Uncertainties Arise From the US Preventive Services Task Force Recommendation on the Diagnosis of Hypertension. *The Journal of Clinical Hypertension*, [e-journal].

Williams, B., Pouter, N.R., Bown, M.J., Davis, M., McInnes, G.T., and Potter, J.F., 2004. British Hypertension Society. Guidelines for Management of Hypertension: Report of the Fourth Working Party of the British Hypertension Society. *Journal of Human Hypertension*, 18(9) pp139 – 185.

Wolff, M., Rogers, K., Erdal, B., Chalmers, J.P., Sundquist, K. and Midlov, P., 2016. Impact of a short home-based yoga programme on blood pressure in patients with hypertension: a randomized controlled trial in primary care. *Journal of human hypertension*, [e-journal]

Wood, S. and Griffith, B., 1997. *Conquering high blood pressure: the complete guide to managing hypertension*. [e-book] Da Capo Press.

World Health Organization, 2005. *Make Every Mother and Child Count: The World Health Report*. [e-book] World Health Organization.

World Health Organization, 2011. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia.

Wu, J., Kraja, A.T., Oberman, A., Lewis, C.E., Ellison, R.C., Arnett, D.K., Heiss, G., Lalouel, J.M., Turner, S.T., Hunt, S.C., Province, M.A. and Rao, D.C., 2005. A summary of effect of antihypertensive medications on measured blood pressure. *American journal of hypertension*, [e-journal] 18 (7), pp.935-942.

Wu, P., van den Berg, C., Alfircvic, Z., O'Brien, S., Röthlisberger, M., Baker, P.N., Kenny, L.C., Kublickiene, K. and Duvekot, J.J., 2015. Early pregnancy biomarkers in pre-eclampsia: A systematic review and meta-analysis. *International journal of molecular sciences*, [e-journal] 16 (9), pp.23035-23056.

Xie, R.H., Guo, Y., Krewski, D., Mattison, D., Nerenberg, K., Walker, M.C and Wen S.W., 2013. Trends in using beta-blockers and methyldopa for hypertensive disorders during

pregnancy in a Canadian population. *European journal of obstetrician gynaecology reproduction biology* 171(2), pp.281-285.

Zamorski, M.A. and Green, L.A., 2001. NHBPEP report on high blood pressure in pregnancy: a summary for family physicians. *American Family Physician*, 64 (2), pp.263-70, 216.

Zatz, R. and Baylis, C., 2000. Nitric oxide and hypertension. [e-book] 2000. *Nitric Oxide and the Regulation of the Peripheral Circulation*. Springer. , pp.99-109.

Zheng, D., Giovannini, R. and Murray, A., 2012. Effect of respiration, talking and small body movements on blood pressure measurement. *Journal of human hypertension*, [e-journal] 26 (7), pp.458-462.

Zheng, D., Amoores, J.N., Mieke, S. and Murray, A., 2011. Estimation of mean arterial pressure from the oscillometric cuff pressure: comparison of different techniques. *Medical & biological engineering & computing*, [e-journal] 49 (1), pp.33-39.

